Official Publication of The American Federation for Clinical Research

Clinical Research Proceedings

VOL. II, NO. 1 MARCH, 1954

IN THIS ISSUE

Published by Grune & Stratton, Inc.

VOL. II, NO. 1 *Clinical Research Proceedings* MARCH 1954

Abstracts Submitted to the Annual Meeting of the Midwestern Section of the American Federation for Clinical Research

Congress Hotel, Chicago, Illinois • Thursday, October 29, 1953

BLOOD

Studies on the Motility Patterns of Lymphocytes. *Robert J. Rohn and William H. Bond.** Indiana University Medical Center, Department of Medicine, Indianapolis.

The morphologic characteristics of lymphocytes in a variety of infectious and neoplastic diseases have been the subject of considerable controversy. Attention has been focused on chromatin patterns, quantity of cytoplasm, mitochondrial activity, and granular prominence, but, to date, little attention has been accorded the motility of these cells.

Present day concepts would suggest that there are: (1) normal lymphocytes, (2) abnormal lymphocytes which are characteristic of infectious mononucleosis, although found also in other viral infections, and (3) abnormal lymphocytes peculiar to (a) acute and (b) chronic lymphocytic leukemias.

In our experience, all standard staining technics interfere with the study of these cells, chiefly by their retardation of cell motility. We have found that the static appearance of stained lymphocytes might lead to erroneous concepts which must be altered after examination of fresh unstained preparations.

It is our observation that the static morphologic pattern of lymphocytes is a result of two factors: (1) maturity and (2) motility. The study of the cellular maturity of lymphocytes is not dependent upon the staining technic used. The use of time-lapse micro movies of unstained lymphocytes, however, has enabled us to study in more precise detail the characteristic motility of lymphocytes in normal individuals and in patients with various disease entities in which there are described lymphocytic abnormalities. From these studies it can be seen that in many cases the characteristic morphologic appearance of a lymphocyte often depends upon its state of motility at any given instant, and that often the same cellular morphology may be seen in different disease states in which lymphocyte motility is similar.

The characteristic motility of lymphocytes in normal individuals and in patients with infectious mononucleosis, pernicious anemia, and acute and chronic lymphocytic leukemia is clearly illustrated in a series of time-lapse micro movies employing supravital and unstained preparations with standard and dark phase illumination.

The Demonstration of Genetic Linkage Between Ovalocytes and the Rh Blood System. *R. A. Marshall,** *Esther Beckner** *and R. M. Bird.* University of Oklahoma, School of Medicine, Oklahoma City.

A family of 31 members has been studied in an attempt to demonstrate genetic linkage in ovalocytosis (elliptical erythrocytes). In 12, 20 to 80% of the erythrocytes were oval. The blood of 26 persons was typed for ABO, MNS, Rh, Lewis, Kell, and Duffy systems. Using unaffected members of the family as controls, evidence for linkage between oval erythrocytes and blood types was demonstrated only in the Rh system.

Blood for typing was taken from 11 of the 12 individuals who showed the oval trait. All of these were of the Rh type $\frac{CDe}{C\text{-}e}$ or $\frac{CDe}{c\text{-}e}$. The comparative data for affected and control members established that the chromosomal distributions for the oval trait and the Rh pattern CDe (R_1) are identical, indicating genetic linkage. A similar conclusion has been recently reached independently by Lawler and coworkers in England.

Although ovalocytosis cannot be considered a disease state in this family, the method of investigation outlined in this study provides a tool which might allow one to predict human matings which might produce a significant incidence of certain familial diseases.

* An asterisk indicates "by invitation."

Time-lapse Micro Cinematographic Studies of the L.E. Phenomenon. *Robert J. Rohn and William H. Bond.** Indiana University Medical Center, Department of Medicine, Indianapolis.

We have previously described our concepts of the formation of the L.E. cell on examination of supravitally stained preparations. It was our concept that the L.E. factor acted in two ways: (1) it initiated premature nuclear autolysis of polymorphonuclear leukocytes which became L.E. bodies, and (2) it promoted phagocytosis of these lysed granulocytes by intact neutrophilic, eosinophilic, and basophilic leukocytes.

This concept is confirmed by time-lapse micro movies of supravitally stained bone marrow preparations. In these sequential studies, formations of rosettes, "signet rings," and clusters typical of this phenomenon are illustrated. These studies illustrate the additional fact that phagocytosis is not complete until at least partial dissolution of the cytoplasmic membrane is presented to the phagocytic leukocyte.

The Erythrophagocytic Properties of Serum from Patients with Acute Disseminated Lupus Erythematosus. *Robert J. Rohn, William H. Bond* and Mary Lou Rish.** Indiana University Medical Center, Department of Medicine, Indianapolis.

Many observers have noted that when L.E. serum is incubated with donor leukocytes from another individual, L.E. cells will be formed. Under certain conditions, however, it has been our experience that this phenomenon is overshadowed or even completely blocked by the development of active erythrophagocytosis.

Our first observation of this phenomenon was made when the serum from a patient with known acute disseminated lupus erythematosus was incubated with leukocytes obtained from a patient with congenital hemolytic anemia. On examination of this preparation it was noted that, while leukocytes contained 1 to many phagocytized erythrocytes and peculiar "clear bodies," careful search failed to reveal a single clearly defined L.E. cell. This phenomenon was then checked by employing known L.E. serum against donor leukocytes from normal individuals and from a considerable number of patients with a variety of disease entities.

When known L.E. serum was incubated with leukocytes from patients with primary and secondary hemolytic anemia, Hodgkin's disease, polycythemia rubra vera, chronic lymphocytic leukemia, leukolymphosarcoma (acute lymphatic leukemia), Gaucher's disease, reticulum cell sarcoma, follicular lymphoma, sarcoidosis, and sickle cell disease, erythrophagocytosis strikingly predominated over formation of L.E. cells.

When, however, known L.E. serum was incubated with donor leukocytes from normal controls, acute bacterial infections, carcinomas (both untreated and irradiated), and thrombocytopenic purpuras, formation of L.E. cells was usual and erythrophagocytosis was rarely observed.

In those preparations in which L.E. serum was incubated with donor leukocytes from patients with chronic myelogenous leukemia, L.E. cell formation and erythrophagocytosis were encountered with equal frequency.

Some speculation as to the cause of this phenomenon and the precursor of the "clear body" is presented, and illustrated by graphs and photomicrographs.

Effect of Specific Antibody on the Phagocytosis of Virus Modified RBC. *D. Shelton Mabry,* John H. Wallace,* Mathew C. Dodd* and Claude-Starr Wright.* Departments of Medicine and Bacteriology, Ohio State University, Columbus.

Normal human, rabbit and chicken erythrocytes were not phagocytized to any significant degree when tested by a recently standardized erythrophagocytic technic using tissue culture macrophages (J. Lab. & Clin. Med. *41:* 169, 1953). Many types of in vitro modifications have the capacity to "opsonize" normal RBC so that they are readily phagocytized. Among these "opsonizing" modifiers are trypsin and other proteolytic enzymes, specific and isohemagglutinins, and various viruses. RBC of some patients with malignancies, certain infectious diseases and hemolytic anemia are also more readily phagocytized than normal RBC. The following studies were part of a continuing inquiry into the fundamental factors influencing the susceptibility of RBC to phagocytosis:

(1) RBC from chickens experimentally infected with Newcastle disease virus (NDV) were phagocytized to the same degree as chicken RBC treated with NDV in vitro.

(2) Normal human group O and normal chicken erythrocytes were modified in vitro by treatment with active NDV for several hours at 37° C. These modified RBC were used to immunize rabbits for the production of an hemagglutinin with specificity for the virus-treated RBC. By absorption technics, serum fractions were obtained and shown to specifically agglutinate erythrocytes treated with NDV in vitro, as well as RBC from NDV infected chickens. Thus, there appears to be a relation between the erythrocyte modification detected by the antiserum and that detected by the phagocytic test.

(3) Phagocytic Indices (PI) for untreated normal group O human RBC and normal untreated chicken RBC were about 10%. The PI of these erythrocytes after treatment with NDV were increased to a range of 65–75%. After further treatment with absorbed anti-virus-treated erythrocyte serum, the NDV modified RBC gave PI of about 10%. Normal rabbit serum had no effect on the PI (70%) of NDV-treated red blood cells. This specific hemagglutinin, then, inhibited the phagocytosis of NDV "opsonized" chicken erythrocytes.

In contrast to the usual "opsonizing" effect of antibody, this immune hemagglutinin reversed the enhanced susceptibility phagocytosis resulting from the modification of RBC by virus.

The Alteration of Ascorbic Acid Oxidation in Pernicious Anemia. *John J. Will, John F. Mueller, Helen S. Glazer,* Ben I. Friedman* and Richard W. Vilter.** University of Cincinnati, College of Medicine, Cincinnati.

The biochemical relationship of ascorbic acid and its oxidation product (dehydroascorbic acid) to hematopoiesis, has not been established. Ascorbic acid seems to be necessary for the conversion of folic to folinic acid. A deficiency of vitamin C plays an important role in the etiology of the megaloblastic anemia of infancy, and minor hematologic responses may occur in pernicious anemia patients fed large doses of ascorbic acid. Furthermore, abnormally low levels of vitamin C have been found in the plasma and white blood cells of persons with pernicious anemia who have had an apparently adequate intake of vitamin C. The latter observation suggests excessive oxidative destruction or utilization of ascorbic acid in the pernicious anemia patient. To test this hypothesis, ascorbic acid and dehydroascorbic acid were determined in 7 patients with pernicious anemia in severe relapse, and in 5 control subjects without hematologic disease. Plasma specimens were obtained before the intravenous administration of 300 mg. of sodium ascorbate and 15 minutes, 1, 2 and 3 hours afterward.

In the control group 15 minute plasma specimens showed a prompt rise of ascorbic acid and a lesser rise of dehydroascorbic acid. Five of 7 pernicious anemia patients showed a reversed relationship with a rise of dehydroascorbic acid and a minimal rise of ascorbic acid. Following specific treatment normal relationships were reestablished.

These results indicate that in 5 of 7 pernicious anemia patients the normal relationship of ascorbic acid to its oxidation product (dehydroascorbic acid) is altered and that this alteration is corrected by specific therapy. The implications of these findings are discussed.

Effect of Vitamin B_{12} and Intrinsic Factor on Maturation of Megaloblasts in Tissue Culture. *Edward H. Reisner, Jr. and Harold T. Swan.** New York.

Using Lajtha's modification of the Osgood technic 10 megaloblastic marrows from pernicious anemia patients and 4 from patients with sprue and a megaloblastic hemolytic anemia (both of which responded clinically to vitamin B_{12}) were cultured for from 1 to 4 days (usually 2), in a medium of pernicious anemia serum alone and with physiologic concentrations of vitamin B_{12}; normal gastric juice or intrinsic factor concentrate; intrinsic factor source and B_{12} together; and, in some instances, folic or folinic acid. The percentages of megaloblasts and normoblasts in smears of each culture were compared with the control.

Maturation occurred in all of the control specimens at a variable rate and was inconstantly affected by the addition of B_{12}, folinic acid or intrinsic factor alone. In 11 of the 14 cultures B_{12} plus intrinsic factor showed less maturing effect than B_{12} alone. In no instance did it show more. In only a few instances were the differences between control and experimental counts statistically significant. However, the probability of the trend shown in the B_{12} plus intrinsic factor cultures appears small. Because of the many variables inherent in the method, the suspension technic is a difficult one with which to obtain clear-cut results. We have not been able to confirm the claims of others that in this medium intrinsic factor enhances the maturing effect of B_{12}. From our observations it appears that, as with bacterial cells, intrinsic factor makes B_{12} less available for use by growing red cells in vitro.

Vitamin B_{12} F: Relative Lack of Antipernicious Anemia Activity. *Robert F. Schilling.* University Hospitals, Madison, Wisconsin.

Several forms of vitamin B_{12} (*a* to *f*) have been described. Those lettered *a* through *e* have been reported to be effective in the treatment of pernicious anemia. Crystalline B_{12f} has been isolated from rat feces by Lewis and Elvehjem. It supports the growth of *L. Leichmannii* in a B_{12} assay medium, but is inactive in the rat assay. This is a report of a trial of B_{12f} in the therapy of 4 patients with achlorhydria and megaloblastic anemia. In each patient daily reticulocyte counts were made during two contiguous 10-day periods. During the first period each received 1 μg. B_{12f} subcutaneously, and during the second each received 1 μg. B_{12} (Cobione, Merck) subcutaneously. The reticulocyte response in the first period was completely absent or very slight, if present at all. The response in the second period was distinctly superior.

The data indicate that the daily injection of 1 μg. B_{12f} is not effective in treating pernicious anemia. 1 μg. B_{12} (Cobione, Merck) produced a definite reticulocyte response in these patients and has been shown previously to be hematopoietic in pernicious anemia.

It is important to realize that microbiologic activity as vitamin B_{12} is not necessarily equivalent to antipernicious anemia activity. Vitamin B_{12} from each new source should be tested clinically before its microbial growth-promoting activity is accepted as indicative of its antipernicious activity.

Early Atypical Manifestations of Leukemia. *Gordon C. Meacham* and Austin S. Weisberger.* Western Reserve University, School of Medicine, Department of Medicine, Cleveland.

The early manifestations of leukemia may be atypical and precede the onset of clinically recog-

nizable leukemia by several years. The purpose of this report is to present the data on 11 patients with similar but atypical hematologic manifestations, 8 of whom developed leukemia. These cases were followed from 1 to 5 years. In addition to those developing leukemia, 1 developed reticulum cell sarcoma, 1 died of aplastic anemia and 1 died of hemorrhage.

All of these patients had severe anemia which was usually hemolytic, although the reticulocytes were not uniformly increased. Nine cases had leukopenia. In every case neutropenia was present. Thrombocytopenia was present in 10 patients. A hyperactive marrow was uniformly present. Nine cases underwent splenectomy without significant benefit. Pathologically, the spleen revealed only passive hyperemia without specific morphologic lesions; in one patient who subsequently developed leukemia, myeloid metaplasia was described in the spleen. Following splenectomy there was an increase in circulating normoblasts in all cases and in 6 patients a significant increase in leucocytes occurred. Therapy with cortisone or ACTH was ineffective.

Of the 8 patients who developed leukemia, 6 were myeloid and 2 were monocytic in type. In each instance the clinical course was rapid after the development of clinically recognizable leukemia. Many features of these cases resemble "hypersplenism" or a syndrome previously described as "aplastic anemia with a hyperplastic marrow." However, these cases differ from the hypersplenic form of panhematopenia in that the spleen is not usually enlarged. In addition, the anemia and thrombocytopenia are more severe than usually encountered in this disease and there is no response to splenectomy. There has been considerable doubt that "aplastic anemia with hyperplastic marrow" represents a distinct entity.

This syndrome of severe anemia—a hyperactive marrow, neutropenia usually with leukopenia, thrombocytopenia and a normal or only slightly enlarged spleen—does not respond to splenectomy. In these cases pathologic examination, except in 1 instance, revealed no lesion suggestive of leukemia. It is important to recognize that these unusual hematologic manifestations frequently are a precursor to leukemia and are not a form of hypersplenism or aplastic anemia.

Clinical Evaluation of 6-Mercaptopurine in the Treatment of Leukemia. *J. H. Burchenal, M. L. Murphy,* R. R. Ellison, M. P. Sykes, D. A. Karnofsky* and T. C. Tan** (introduced by *Frank H. Bethell*). Chemotherapy Service of Memorial Center for Cancer and Allied Diseases and the Division of Experimental Chemotherapy of Sloan-Kettering Institute for Cancer Research, New York.

A new antimetabolite, 6-mercaptopurine (6MP), has been shown to cause temporary remissions in a substantial percentage of children and an occasional adult with acute leukemia. In children, little or no toxicity occurred at the usual therapeutic dosage of 2.5 mg./Kg. daily orally, but prolonged treatment at this level in adults or at higher levels in children occasionally caused bone marrow depression or gastrointestinal disturbances. Remissions lasting 2 to 6 months occurred after 3 to 8 weeks of therapy in both high and low count leukemias, and in those resistant to cortisone and amethopterin, as well as in previously untreated cases.

Of 65 children with acute leukemia, clinical and hematologic remissions were achieved in 26 patients, partial remissions in 11, and no remission in 28. Of the 40 adults, 5 (aged 15, 21, 21, 35 and 52 years respectively) had clinical and hematologic remissions and another 6 showed considerable clinical benefit with some improvement of marrow and peripheral blood. Twenty-nine were considered failures.

Remissions were achieved in all 8 patients in the early stages of chronic myelocytic leukemia. Two of these have now been treated on maintenance therapy with the drug for 9 and 11 months, respectively. In one, in the late stage with generalized lymphadenopathy, and in two, in the terminal acute stage of the disease, temporary remissions were achieved.

In hopes of delaying the development of resistance to 6MP in the acute leukemias, combinations of this drug with various other chemotherapeutic agents are under study.

Rectal Administration of Urethane in Treatment of Chronic Leukemias and Multiple Myeloma. *Leif G. Suhrland* and Austin S. Weisberger.* Cleveland.

Oral administration of urethane frequently is accompanied by nausea, vomiting or diarrhea, necessitating withdrawal of the drug. Therefore, the efficacy of rectal administration of urethane was investigated.

Nineteen patients were treated with rectal suppositories of urethane in doses ranging from 3 to 6 Gm. daily. In 8 patients with chronic myeloid leukemia, 6 had excellent remissions. Two patients who did not respond were in the terminal blastic phase of the disease. In 4 patients with chronic lymphatic leukemia, only 1 responded with a fall in leukocyte count to near normal level and regression of lymph nodes and spleen. In 7 patients with multiple myeloma, 3 had a good subjective response with disappearance of bone pain and an increase in well-being. Two patients had some diminution of bone pain and 2 patients had no response. One patient with multiple myeloma developed myxedema after 12 months of treatment. Thyroxin aggravated the original complaints and resumption of the myxedematous state resulted in amelioration of

symptoms. Preliminary studies indicate that urethane may depress uptake of I^{131}.

Of the 19 patients treated for periods varying from 2 weeks to 22 months only 1 patient developed diarrhea, necessitating withdrawal of the drug. No instances of rectal irritation occurred. Other side effects were absent except for mild nausea in 1 patient who received 6 Gm. of urethane daily.

It is concluded that rectal administration of urethane is preferable to oral or intravenous administration.

The Effectiveness of Water and Oil-Soluble Vitamin K Preparations in Correcting Hypoprothrombinemia. *John R. Gamble,* Edward W. Dennis, William W. Coon,* Paul Hodgson,* Jack A. MaCris,* Park W. Willis* and Ivan F. Duff.* Ann Arbor, Michigan.

Oil-soluble vitamin K_1 (Methyton) is an effective antagonist to the effect of oral anticoagulants (both coumarin and indandione derivatives). Vitamin K_1 appears equally effective orally or intravenously. Cessation of hemorrhage and safe prothrombin levels resulted in 40 out of 44 trials within 20 hours. A single oral dose of vitamin K_1 varying from 5 to 25 mg. was effective in 15 out of 17 trials. In 20 out of 22 trials 50 mg. or less of intravenous K_1 was satisfactory in 20 hours or less. There were 4 instances in which above dosages by either route proved ineffective. Untoward complications to excessive dosages of vitamin K_1 have not occurred; minimal yet effective dosages of K_1 are desirable to avoid refractoriness, if use of anticoagulants is resumed later. In contrast to K_1, the water-soluble preparation of vitamin K (menadione bisulfite, Hykinone), is not consistently reliable as an antidote to the oral anticoagulants. With a dosage of 40–144 mg. of Hykinone, safe prothrombin levels occurred in only 11 out of 26 trials in 24 hours with 3 more responding in 48 hours.

Response to vitamin K cannot be predicted with certainty with hypoprothrombinemia secondary to severe hepatic disease. There may be a gradual rise of the prothrombin to a final level which often falls short of the normal value after 50 mg. vitamin K_1 intravenously, repeated 3 times in 1 week. In correction of hypoprothrombinemia due to absorptive difficulties, 5 mg. of K_1 and 72 mg. of Hykinone intravenously produced normal prothrombin levels in as little as 4 hours.

Clinical Evaluation of Dipaxin, an Oral Anticoagulant. *Park W. Willis, III,* Jack A. MaCris,* Edward W. Dennis, Paul E. Hodgson,* William W. Coon,* John R. Gamble,* and Ivan F. Duff.* Ann Arbor, Michigan.

Dipaxin, 2-diphenylacetyl-1,2-diketo-hydrinene, has been administered orally to 104 individuals of whom 64 had normal prothrombin values (Quick method). Comparison is made in table I of patients treated with other oral anticoagulants.

TABLE I

	Dipaxin	Phenylindandione	Dicumarol	Tromexan
No. patients	64	133	122	50
Mean effective dose, mg.	63	685	646	3120
Therapeutic effect:				
within 48 hrs.	67%	95%	55%	82%
average (days)	2.3	1.3	2.3	2.1
Av. recovery time to 40% (days)	4.1	1.5	5.0	2.5
Prothrombin incid.:				
escape above 30%	38%	17%	37%	90%
fall below 10%	10%	10%	15%	20%
Bleeding incid.	11% (104 cases)	6.5% (200 cases)	11% (303 cases)	9% (100 cases)

The initial dose of Dipaxin was 30 mg. followed by 40 mg. in 3 doses over the next 36 hours; the average dose required to maintain prothrombin concentration below 30% was 5 to 10 mg. daily. In 2 patients large doses of Dipaxin had no significant effect upon prothrombin concentration; both subsequently responded satisfactorily to phenylindandione (Parke, Davis). When bleeding occurred, hypoprothrombinemia was usually quickly reversed by intravenous or oral vitamin K_1. Albuminuria was not observed. Repeated renal function tests in 2 individuals showed no abnormality.

CARDIOVASCULAR SYSTEM

The Effect of Exercise on the Blood Pressure and Pulse Rate in Normal Subjects. *Robert S. Fraser* and Carleton B. Chapman.* University of Minnesota, Medical School, Minneapolis.

The effect of exercise on blood pressure in normal human beings is still a subject of considerable controversy, partly because indirect sphygmomanometry yields inaccurate results during and immediately after exercise. In an effort to identify accurately the changes that take place under these conditions, direct intra-arterial recording of blood pressure before, during, and after a fixed load of exercise was carried out in 19 young men (aged 18–39), 11 young women (aged 22–30), and 11 older men (aged 40–57). The recording system is mechanically damped so that a flat frequency response

to 19 cycles per second was obtained. A motor driven treadmill, operating at 3 mph and set at 5% grade was used for the exercise. Measurements were made before the beginning, and after exactly 10 minutes, of exercise, but without stopping the treadmill. Continuous records were made during the first minute of recovery and for the first 20 seconds of the succeeding 5 minutes thereafter.

It was found that during exercise the systolic pressure rises significantly, the diastolic falls, and the mean remains approximately unchanged. In the first few seconds after stopping exercise, the systolic pressure fell precipitously in the male subjects but decreased more gradually in the women. In the older men, there was a significant "rebound" rise in the interval 10 to 40 seconds after cessation of exercise. The phenomenon involved all 3 pressure items. In all 3 groups, at the beginning of the sixth minute of recovery, the systolic pressure was close to or less than the resting value; the diastolic had exceeded the resting value and the mean was about the same as during rest.

The increase in pulse rate during exercise was similar in magnitude in all 3 groups. Pulse rates had not returned to resting values by the sixth minute of recovery.

If, as has been suggested, the response of the blood pressure to exercise is to be used for various diagnostic purposes, attention must be paid to differences in response that are probably attributable to age and sex factors, rather than to disease.

Cardiopulmonary Evaluation during Graded Exercise of Normals and Patients with Heart and Lung Disease. *S. R. Inkley, H. K. Hellerstein* and T. W. Moir.** University Hospitals, Cleveland.

Sixty-five subjects, predominantly cardiac (aged 26–79), were studied during treadmill exercise at 1.7 mph on a 10% slope. Ballistocardiograms, resting electrocardiograms, vital capacity and maximum breathing capacity were performed before exercise.

The normal response was characterized by increased respiratory efficiency, decreased ventilatory equivalent, respiratory rate less than 22 per minute, heart rate not exceeding 125 during exercise, lowered T wave, and oxygen debt less than 10%. Fitness Index (Bruce) was determined for all subjects.

Oxygen consumption during exercise varied with body weight, within expected variations, due to difference in muscular efficiency. Oxygen transport correlated with FI, and, in all cases of FI below 10, oxygen transport was less than 6. There was good correlation between low FI and pulse in excess of 12.5 during exercise. Maximum breathing capacity, vital capacity and ballistocardiogram were not strikingly related to FI in this series.

The purpose of the study has been twofold: (1) to correlate fitness in everyday life with measured fitness on the treadmill, and (2) to determine, if possible, means of dissecting heart from lung disease during periods of stress. We have noted exceptions to the correlation between the fitness index and everyday fitness. In such cases the requirements of everyday life and gainful occupation are less than those of the treadmill test. Although severe disease of either the heart or lungs may be manifested by specific functional changes during exercise, it is often impossible to differentiate between the two with current technics.

The Effect of Thoracocervical Vagectomy on Cardiovascular Response to Exercise. *Robert S. Fraser* and Carleton B. Chapman.* Department of Medicine and Variety Club Heart Hospital, University of Minnesota, Minneapolis.

Cardiac Rate in the human being is thought to be regulated by interaction of vagal and sympathetic impulses, the former presumably being dominant. Physiologic studies on a patient in whom about ¾ of the vagal pathways to the heart were surgically abolished are of interest in this connection. There was an immediate and permanent increase in resting pulse rate from about 74 beats per minute preoperatively to 120 afterward. Atropine caused no increase in postoperative rate. Resting cardiac output (dye dilution method) was normal 4 months after surgery. Response of cardiac output to a standard treadmill load was also normal, the increase being about 1.9 times. In normal subjects working at the same rate the increase is 1.7 to 1.9 times. The patient's increase in pulse rate during exercise, however, was significantly less than normal. The response of blood pressure to exercise was the same as that observed in the normal group.

It is concluded that absence of most, or all, of normal vagal pathways to the heart modifies, but does not abolish, the ability of the cardiovascular system to respond effectively to moderate exercise. The possibility is raised that nonvagal influences may come into play under these circumstances.

Extended Time-base Analysis of Heart Sounds and Murmurs. *Simon Rodbard.* Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago.

Studies of the characteristics of flow through collapsible vessels simulating valves have suggested that heart and vessel murmurs are composed of recurrent bursts of sounds. Efforts to test this concept have provided an approach to the ultrastructure of these sounds. Sounds were picked up with a standard high impedance Rochelle crystal microphone, and passed through a filter which cut off all frequencies below 500 cycles per second. After preamplification the sounds were recorded on tape at 15 inches per second. The tape was then played at ⅛ the original speed, the sounds being recorded on sensitized paper by galvanometer. The low fre-

quency components were thus eliminated, and the high frequencies were augmented. The time-base was stretched by a factor of 8. The heart sounds were now heard as a series of recurrent bursts of noise, much like the noise produced by drawing a stick along a picket fence. These bursts could be separated into groups suggesting that the first heart sound was composed of 2 to 4 discrete noises. The second heart sound had a similar divided structure. Heart murmurs such as aortic stenosis and those due to patent ductus arteriosus were recorded as recurrent bursts at a rate of 100 to 200 per second. Korotkoff sounds had a similar structure. These data are compatible with the concept that murmurs are produced by high velocity flow through relatively collapsible orifices or tubes. A study of the hydrodynamics of such flow might thus be expected to provide information concerning the dynamics genesis and clinical significance of these sounds.

Clinical and Laboratory Correlation of the Ballistocardiogram. *Frank J. Kelly and George W. Curd, Jr.** Veterans Administration Hospital and the Department of Medicine, Baylor University College of Medicine, Houston.

In view of the rapidly expanding clinical use of ballistocardiography, the following observations on 600 hospitalized patients seem worthy of recording. The electromagnetic (Dock type) instrument containing a 70 microfarad condenser was used and tracings recorded by means of a Cambridge string galvanometer. Records were made in the supine position during quiet respiration and while the breath was held in inspiration and in expiration. The criteria and grading system of Brown, Hoffman and De Lalla were used.

Among 204 patients without clinical, electrocardiographic or Roentgenographic evidence of heart disease or conditions which might affect the cardiovascular system, 67% of those under 40 years of age and 19% of those over 40 years of age had "normal or borderline" ballistocardiograms. Grade 1 or 2 ballistocardiograms were observed in 25% under 40 and 40% over 40 years, and grade 3 or 4 ballistocardiograms noted in 9% of those under 40 and in 41% of those over 40 years of age. Among 42 patients with myocardial infarction (7 under 40 years of age) 5% had "normal" ballistocardiograms, 19% grade 1 or 2, and 76% grade 3 or 4 tracings. Fourteen cases of essential hypertension presented the same type of distribution of ballistocardiograms as did the "normal" group. In a group of 46 patients with hypertensive heart disease, 70% of whom were over 40 years of age, the following ballistocardiograms were noted: 12% "normal," 33% grade 1–2, and 55% grade 3–4. Thirty six patients with valvular heart disease, symptomatic in most cases, presented the following types of ballistocardiograms: those under 40 years of age, 70% "normal," 30% grade 1 or 2, and 0% grade 3 or 4; over 40 years of age, 19% "normal," 42% grade 1 or 2, and 39% grade 3 or 4. All those patients having aortic insufficiency with or without other lesions, and with or without failure, had "normal" or grade 1 ballistocardiograms, with one exception who also had a myocardial infarction.

The effects of nitroglycerine and of changes in serum electrolyte concentration will be discussed. Of interest were two patients with coarctation of the aorta who demonstrated loss of characteristic ballistocardiogram alterations following nitroglycerine.

A Study of 1000 Electrocardiograms in Males, Correlating the Effects of Age, Obesity and Hypertension. *Raymond Pearson.* Springfield, Illinois.

This study of one thousand living males attempts to correlate age, weight and hypertension in relation to complete electrocardiographic studies. Interest in the effects of age, weight and hypertension on longevity have been intensively studied by insurance companies with well known conclusions. From this data it seemed logical to assume that similar findings would prevail on a large clinical group. One thousand males were given a complete physical examination. X-ray of the chest, 12 lead electrocardiogram, measurements of blood pressure in three positions, and height and weight were recorded.

Using the table of the Metropolitan Life Insurance Company for normal height and weight, each individual was placed into one of three large groups: (a) underweight, (b) normal weight, (c) overweight which was further subdivided into percentage groups increasing by 10% increments. All electrocardiograms were interpreted by this observer and diagnoses listed.

Over 80% of the males in this group were between 50 and 70 years of age although there were about 50 in each decade from 20 to 50 years of age. The number above 70 was small. Thus, this group falls mainly into the ischemic heart disease group. With increasing age, the number of abnormal electrocardiograms remained fairly constant up to 70 years of age, after which the percentage of abnormals rises abruptly. Particularly in the age groups with large numbers (50–70 years), the percentage of abnormals was the same. Aging did not seem to increase the percentage of abnormal electrocardiograms up to 70 years of age, as would be expected by mortality statistics.

A study of the effects of increasing degrees of obesity revealed that only a small, probably insignificant, rise occurred in the number of abnormal electrocardiograms as weight increased up to 70% above normal. Thus, the electrocardiographic abnormalities do not seem to increase in number as weight increases up to the limits studied.

Hypertension was studied in relation to abnormal electrocardiograms and it was found that the

frequency of abnormal electrocardiograms doubled with the presence of hypertension (defined as 170/100 or greater).

Finally, a comparison was made of those who had hypertension (170/100 or over) and obesity (defined as weight greater than 20% above normal) with the number having normal and abnormal electrocardiograms. The group included 106 males meeting this criteria and 48% had abnormal electrocardiograms, or about the same percentage as for the hypertensive group alone.

A Study of Pulsus Alternans. *Joseph M. Ryan, James F. Schieve and Hugh B. Hull.* Department of Medicine, College of Medicine, Ohio State University, Columbus.

During an investigation of pulsus alternans it was found that this phenomenon could at times be rather profoundly influenced by changes in the venous return to the heart.

Twenty patients with organic heart disease characterized by left ventricular enlargement form the basis of this study. The direct arterial pulse, heart sounds and electrocardiogram were recorded simultaneously.

Only 2 patients had established alternans. Exercise and passive leg raising lessened the degree of alternans in these subjects, whereas venous tourniquets and sudden tilting to the upright position exaggerated this phenomenon. Pulmonary arterial pressures recorded simultaneously with the peripheral pulse in one of these subjects showed this phenomenon to be limited to the left side of the circulation. In only one of 18 patients did the stress of exercise bring out an alternans when it was absent at rest. Venous tourniquets also caused pulsus alternans in this patient to an even greater degree than did exercise. The occurrence of short runs of alternation following a ventricular premature beat was noted in 6 patients, the duration of this alternation being related to the state of the venous returns in the same manner as established alternans.

These observations suggest that decreasing the venous return to the heart will accentuate pulsus alternans, and that increasing venous return will diminish it. These observations further suggest that pulsus alternans might be more easily detected clinically if the patient is upright.

The Effect of Atropine on the Apical Rate of Auricular Fibrillation Controlled with Acetyl Strophanthidin. *Richard W. Dyke* and Charles Fisch.* Robert M. Moore Heart Clinic, Indianapolis General Hospital, Indianapolis, and the Department of Medicine, Indiana University School of Medicine.

Acetyl strophanthidin, a synthetic derivative of *Strophanthus kombe* has been shown by Chen and Elderfield and others to have digitalis-like action.

Twenty patients with auricular fibrillation and ventricular rates over 100 beats per minute were given the drug intravenously. The dose varied from 1.5 cat units to 3.0 cat units given at 10–15 minute intervals until the desired effect was obtained. Electrocardiographic record was taken every 1–3 minutes. After maximum slowing was attained, 1.25 mg. of atropine was administered intravenously.

Uniform slowing of the ventricular rate was observed in all patients. Administration of atropine caused significant acceleration of the heart rate only in those patients who were given the drug in doses which were considered too small to exert an extravagal effect. Side effects consisted of vomiting in 1 patient and appearance of premature beats in 6 subjects.

The value of the drug in clinical medicine and the significance of response to atropine as index of extravagal effect of the drug will be discussed. The indications and contra-indications will be stressed.

Familial Incidence of Congenital Heart Disease. *Frank R. Hanrahan* and Henry A. Zimmerman.* Cardiopulmonary Laboratory, Charity Hospital, Cleveland.

Much has been written recently of cardiovascular disease and the relation of virus infections, especially measles, during the first two months of pregnancy, to congenital heart disease. Doubt has recently been cast upon this theory, and we wish to further emphasize the importance of heredity as the basic factor in congenital heart disorders.

Taussig states that if a congenital malformation occurs in one offspring, there is a 20% chance that there will be some abnormality in the subsequent offspring by the same mating, and a 2% chance of reoccurrence of the identical malformation.

Until 1940, however, only 49 families with multiple instances of congenital malformations of the heart had been reported. It is the purpose of this paper to add a group of 4 such families: the first with 4 children, 3 of whom are boys who have cleft palate, hare lip, and congenital heart disease; the second with 2 children, who have congenitally malformed hearts; the third in which the boy and a sister, 1 of twin girls, have heart disease; and the fourth, in which both children, a boy and a girl, are afflicted.

We feel that the finding of multiple congenital heart disease in the same family is much commoner than has been reported in the literature, and that the hereditary aspect of the problem is in need of emphasis.

Essential Telangiectasia, Pulmonic and Tricuspid Stenosis and Neoplastic Liver Disease. A Possible New Clinical Syndrome. *Daniel G. Santer,* Francis F. Rosenbaum and Dann B. Claudon.** Milwaukee.

Two patients who were observed over a period of several years until their death presented an

unusual combination of clinical and pathologic manifestations which seemed to indicate that a hitherto unreported clinical syndrome may have been encountered. The second case resembled the first so closely that the correct diagnosis was made antemortem. The initial and most striking clinical feature was a profound telangiectasis appearing first on the face, later extending to the thorax, abdomen and upper extremities, and ultimately becoming so severe that the face took on a frightening, purple-grey hue. The first evidence of telangiectasis preceded death by 20 years in one patient and by 10 years in the other. Histologic studies of the skin from the involved areas disclosed greatly dilated veins considered to be pre-existing rather than newly formed veins and capillaries.

The later years of life were characterized by progressive congestive heart failure, primarily right ventricular in origin. Postmortem examination disclosed severe pulmonic and tricuspid stenosis with minor mitral valvular involvement in each patient. The valvular disease was considered of rheumatic origin, although Aschoff's bodies were found in only one case. Hepatomegaly preceded death by 10 years in one patient and 2 years in the other. There were extensive hepatic metastases from a carcinoid of the ileum in the former, and an extensive adenocarcinoma of the hepatic bile ducts in the latter.

The venous pressures which were recorded in these patients did not appear of sufficient magnitude to produce this type of dilatation of the capillaries and venules. The telangiectasis was of such great duration that, in all probability, it antedated the hepatic disease. The telangiectasis, therefore, remains unexplained although it may have been the end result of some peculiar capillary damage due to the initial rheumatic disease which also produced the unusual valvular disturbance.

The Pulmonary Hemodynamic Pattern in Patients with Atrial Septal Defects before and after Closure. *S. Gilbert Blount, Jr., Goffredo Gensini and Malcolm C. McCord.* Denver.

Twenty patients evaluated by cardiac catheterization were divided into two groups in an attempt to investigate factors leading to the development of pulmonary hypertension. Group I consisted of 11 asymptomatic patients with an average mean pulmonary artery pressure of 15 mm. Hg. Microscopic examination of lung tissue in 3 patients showed normal vasculature. Group II was comprised of 9 patients with an average mean pulmonary artery pressure of 43 mm. Hg, 7 of whom were symptomatic. Microscopic examination showed pulmonary vascular changes in 2 patients.

A comparison of the 2 groups showed an identical average age, a greater average pulmonary flow in Group I, 13.6 L./min./M², than in Group II, 9.8 L./min./M², and a lesser pulmonary artery resistance in Group I, 124 dynes/sec./cm.$^{-5}$, than in Group II, 352 dynes/sec./cm.$^{-5}$. Thus, no satisfactory criteria for the prediction of the development of pulmonary hypertension was apparent.

Complete closure of the atrial septal defect was accomplished in 3 patients under direct vision employing hypothermia. Postoperative evaluation of these patients revealed a normal oxygen saturation of the mixed venous blood within the pulmonary artery, no evidence of a left to right shunt at the atrial level, and normal pressures.

The pulmonary arterial pressure in one patient decreased from 100/30 mm. Hg, to 30/17 mm. Hg, the pulmonary flow from 8.9 L./min./M² to 3.0 L., and the pulmonary arteriolar resistance from 253 dynes/sec./cm.$^{-5}$ to 208 dynes/sec./cm.$^{-5}$.

It would appear that pulmonary hypertension can be prevented and existing pulmonary hypertension can be strikingly reduced by closure of an atrial septal defect.

The Indications and Contraindications for Surgical Correction of Intra-Atrial Septal Defects. *Henry A. Zimmerman and Earle B. Kay.** Cleveland.

From experience gained in a series of 15 cases of surgical closure of an intra-atrial septal defect, we feel there are definite indications and contraindications for this procedure.

The indications for closure of an intra-atrial septal defect are: (1) the correct diagnosis and, (2) a patient in the young age group who has not as yet developed irreversible pulmonary arterial vascular changes.

It would appear then that early diagnosis and closures are a prime requisite for excellent results. We feel that definite contraindications are well defined and are, in brief, as follows: (1) patients in the third or fourth decade who have high degree of cyanosis with arterial O_2 saturation of 85 or less, (2) patients with marked elevation of pulmonary arterial pressures, especially those with high diastolic pressures, (3) patients with systolic pressures over 75 mm. of Hg and 35–40 mm. of Hg diastolic pressure should not be repaired.

We also feel that patients with advanced cardiomegaly—20% or more, with or without congestive cardiac failure—add greatly to the mortality in this procedure.

The Pathologic Physiology and Diagnostic Significance of Pressure Pulses in the Right Heart in Patients with Chronic Constrictive Pericarditis and Pericardial Effusion. *Russell H. Wilson, Craig W. Borden, Wayne Hoseth,* Charles N. Sadoff,* and Mary E. Dempsey.** Minneapolis V. A. Hospital, Minneapolis.

The diagnostic criteria of pericardial disease determined by right heart catheterization have been considered to be a high ratio of the ventricular diastolic to systolic pressures, and an early diastolic

dip in pressure, with a high diastolic pressure plateau in the right ventricular pulse tracing.

The purpose of this study was to determine the differences in the pathologic physiology of the pressure pulses in the right side of the heart in pericardial disease and other cardiac diseases causing similar clinical syndromes.

The hearts were catheterized by the methods of Cournand, and cardiac outputs were measured with the direct Fick principle. Pressure pulse tracings from 286 patients with congenital heart disease, 100 patients with rheumatic mitral valvular disease, and 100 patients with other miscellaneous types of cardiac disease were analyzed for the presence of an early diastolic dip or pressure fall and a quick rise to form a high diastolic plateau. A significant pressure dip and high late diastolic plateau were found in 14 patients with congenital cardiac disease, 9 patients with rheumatic mitral valvular disease, and 1 in the miscellaneous group of heart disease. The ratio of the right ventricular diastolic to systolic pressure was calculated in all cases. The range of the ratios was found to be 40% to 58% in all 12 patients with pericardial disease. There were only 10 of the 486 patients with other types of heart disease with corresponding ratios over 33%, 7 with congenital heart disease, 3 with mitral valvular disease, and none of those with miscellaneous types of heart disease. These ratios ranged from 35% to 80%. Therefore, a ratio over 33% is not specific for pericardial disease but is found in other types of heart disease. The diastolic pressure gradients among the superior vena cava, right atrium, right ventricle and pulmonary artery were found to decrease with increasing severity of the chronic constrictive pericarditis and pericardial effusion. The pulmonary arterial wedge pressure reflecting the left atrial pressure was found to approximate the diastolic pressure in the pulmonary arterial trunk in patients with pericardial disease.

Characteristics of Left Atrial Pressure Pulse Waves Recorded at Thoracotomy from Normal Human Hearts and from those with Mitral Stenosis and Regurgitation. *George N. Bedell,* John B. Wild,* Johann L. Ehrenhaft* and James W. Culbertson.* State University of Iowa, Department of Internal Medicine, Iowa City.

Accurate characterization of left atrial pressure pulse waves is prerequisite to direct hemodynamic study of mitral disease. Therefore, at thoracotomy such waves have been recorded electronically through a catheter in 36 patients: 2 with normal hearts, 29 with predominant stenosis and 5 with predominant regurgitation.

The normal pattern began with a gentle auricular contraction wave, *a*. Superimposed on its downstroke, beginning about 0.04 sec. after the R peak, was a sharp and narrow mitral closure wave, *c*. Beginning about 0.15 sec. after the R peak, a gentle and broad atrial filling wave, *f*, followed.

In predominant mitral stenosis with sinus rhythm four patterns appeared: (1) Normal configuration at supernormal pressure levels. (2) Same with interpolation of a small regurgitant wave, *r*, between *a* and *f*. (3) Incorporation of *c* and *r* into a single larger wave. (4) Fusion of *a*, *r* and *f*, with tendency to loss of *c*.

Patients with predominant stenosis and auricular fibrillation had patterns similar to (3) and (4) without *a* waves. A fifth pattern of smoothly undulating single waves was found in this group.

Two patients with predominant regurgitation and sinus rhythm showed a small *a* wave followed by a tall, smooth, fused *r-f* wave beginning shortly after the R peak. Tracings from 3 patients with predominant regurgitation and auricular fibrillation resembled patterns (4) and (5), but without *a* waves.

Efforts are being made to establish morphologic criteria for quantitating at thoracotomy the degree of regurgitation which should contraindicate manipulation of the mitral valve.

Alveolar Carbon Dioxide Levels during Mitral Valve Surgery. *George A. Saxton, Jr., Norman Tate* and William Derrick.** University of Illinois, College of Medicine, Chicago.

Continuous measurements of alveolar carbon dioxide concentration were made with an infrared CO_2 analyzer in 20 cases of mitral valve surgery with assisted respiration. These readings were compared with analyses of blood sampled simultaneously from a peripheral artery or the left auricle. The blood samples were analyzed for pH, CO_2 content and P_{CO_2}. Respiratory minute volume was measured with a gas volume meter in the anesthesia circuit.

The average alveolor CO_2 concentration was found to be normal or low in all cases. The lowest values were observed during the manipulation of the mitral valve, the highest during reinflation of the left lung with increased positive pressure in the airway. The blood analyses were in agreement with the alveolor gas values before the chest was opened, but revealed varying degrees of increased arterial P_{CO_2}, as compared with alveolor P_{CO_2}, at different stages during the open-chest procedure. The gas volume meter recorded changes in pulmonary ventilation consistent with the alveolor CO_2 measurements.

These results were interpreted as indicating: (1) that those areas of the lungs which were not collapsed during open-chest surgery were hyperventilated in order to compensate for the continuing perfusion of the collapsed areas which resulted in venous admixture of arterial blood, (2) chemical stimuli to pulmonary ventilation are more a function of tissue gas tensions in the chemoreceptors and

respiratory center than of arterial gas tensions, (3) pulmonary hypertension reduces significantly the ventilation produced by increased intermittent positive pressure.

Myocardial Ischemia during Mitral Commissurotomy. *J. Gerard Mudd, John J. Inkley and C. Rollins Hanlon.** St. Louis University Hospital, St. Louis.

From an electrocardiographic study of 30 patients undergoing surgery for mitral stenosis, we will present the records of 5 patients who showed electrocardiographic evidence of myocardial ischemia. This is believed due to pressure of the auricular clamp against the left coronary artery. The acute pattern of Q wave deflection and RST-T change of anterior coronary infarction is demonstrated with immediate relief of the acute condition upon informing the surgical assistant to readjust the position of the clamp. The ischemic changes with ST-T segment changes may remain for days with eventual clearing and no subjective symptoms. Two cases of transient ventricular fibrillation resulted. It is suggested that it is advisable to have available electrocardiographic monitoring during the interval of actual surgery upon the left auricle, especially while the clamp is applied to the auricular appendage, and it seems pertinent to stress the value of these electrocardiographic changes as a premonitory sign of impending ventricular fibrillation during mitral commissurotomy.

Cardiac Enlargement Following Mitral Commissurotomy. *Jacob Zatuchni and Louis A. Soloff.* Departments of Medicine, Temple University Medical School and Hospital, and Episcopal Hospital, Philadelphia.

Cardiac enlargement is generally accepted as anatomic evidence of an undesirable load that has been imposed upon the heart. For this reason, careful comparable serial roentgenograms of the cardiac silhouette were made of 36 consecutive individuals subjected to mitral commissurotomy. Of these, 6 died and 12 could not be followed long enough because of geographic or other reasons.

Immediately following operation, there is universal moderate to massive enlargement of the cardiac silhouette, which is attributed primarily to a pericardial reaction and possibly also a myocardial reaction. Following this immediate reaction, the cardiac silhouette gradually shrinks in size, reaching its minimal size within 6 months. For this reason, 6 months was regarded as the arbitrary time to determine the reaction of the heart size to surgery. Disregarding the occasional, and, at times, transient disappearance of the second convex segment along the left border of the heart (presumably due to amputation of the left auricular appendage), roentgenograms of 18 individuals, taken 6 months or more after mitral commissurotomy, revealed that 4 hearts were similar to the preoperative size, 3 slightly smaller and 11 larger.

These findings are interpreted in the light of: (1) precipitating causes of failure preceding operation, (2) rheumatic activation and (3) surgical production of mitral regurgitation.

Rate of Change of Arterial Saturation and Skin Oxygen Tension with O_2 Inhalation in Mitral Stenosis. *Raymond Penneys and Harry F. Zinsser, Jr.* Vascular and Cardiac Sections, Robinette Foundation, Hospital of the University of Pennsylvania, Philadelphia.

Oxygen was administered to patients with mitral stenosis and to normal subjects. The time required for the initial change in arterial oxygen saturation was measured by the oximeter ("lung-to-ear" circulation time). The rate of "build-up" of oxygen tension in the (warm, vasodilated) skin was measured polarographically by the platinum tipped oxygen electrode. As determined by these 2 measurements there was, on the average, a delay in oxygenation in the patients with mitral stenosis, as compared with the normal subjects. The lung-to-ear time was 7.9 seconds in the normals (70 experiments, 19 subjects) and 11.4 seconds in the patients (27 experiments, 14 subjects). In the oxygen tension experiments the delay in oxygenation in the patients with mitral stenosis, as compared with the normal subjects, was manifested by smaller percentages of experiments reaching final equilibrium at various times throughout the period of oxygen inhalation. In the normals (29 experiments, 6 subjects), 17% of the oxygen tension experiments reached equilibrium at 200 seconds, 52% at 300, 76% at 400 and 87% at 500 seconds. In patients with mitral stenosis (23 experiments, 6 patients), only 9% were stable at 200 seconds, 13% at 300, 41% at 400 and 71% at 500 seconds.

An Investigation of the Role of the Pulmonary Arterial Oxygen Content in the Genesis of Pulmonary Hypertension. *S. Gilbert Blount, Jr. and Malcolm C. McCord.* University of Colorado, Department of Medicine, Denver.

Hypoxia and exercise uniformly produce an increase in pulmonary artery pressure in patients with existing pulmonary artery hypertension. Observations on 28 patients have been analyzed in an attempt to define the factors responsible for this pressure rise.

Determinations of pulmonary "capillary" pressure and calculation of pulmonary arteriolar resistance indicated dynamic changes occurring at a pre-"capillary" level, eliminating pulmonary venous pressure rise as the major factor producing the pulmonary arterial pressure elevation.

Elimination of increased blood flow as the dominant element in pulmonary arterial pressure elevation was possible by the demonstration of an

average mean pulmonary artery pressure elevation from 51 to 74 mm. Hg in 7 patients showing no significant change in the cardiac output after exercise. A similar pattern was observed in 6 patients subjected to hypoxia.

An alteration in the caliber of "tonus" of the smaller pulmonary arteries was thus presented as a probable factor. The possibility that the oxygen content of the blood or alveolar air effected these changes in tonus was evaluated. There was no correlation between the pulmonary artery pressure change and the oxygen content of the arterial blood, or the pulmonary alveolar oxygen pressure. There was a constant correlation between the pulmonary artery pressure change and the oxygen saturation of the mixed venous blood.

It is therefore proposed that a primary factor in the production of pulmonary hypertension is the direct effect of the oxygen content of the mixed venous blood on the pulmonary "arterioles."

Physiologic Measurements in Cor Pulmonale. *Timothy R. Murphy,* Jules Chase, Ned Maxell* and Julius Meyer.** Cardiovascular Section of the Medical Department, Marquette University School of Medicine and the Cardiac Service of the VA Hospital, Wood, Wisconsin.

Sixteen patients with the clinical diagnosis of cor pulmonale, secondary to emphysema, were studied by means of cardiac catheterization. This study was based on the determination of the cardiac output in patients with pulmonary emphysema requiring hospitalization, and in whom the diagnosis of cor pulmonale was suspected.

The majority of the patients were in the 5th and 6th decades, with the ages varying between 35 and 70. Total lung volume studies were performed in 10, with residual air varying between 44 and 78%. Arterial oxygen saturations were normal in 4 and abnormal in 12 patients.

Pulmonary artery hypertension was present in 13 patients at rest, and in all patients with moderate exercise. Capillary pressures were measured in 12 patients and were normal.

Resting cardiac indexes ranged from 2.1 to 4.2 L./M^2. All but one of the patients had a cardiac index below 3.5 L./M.^{2}, the highest cardiac index being 4.2 L./M^2. Duplicate resting cardiac outputs were performed in some of the patients, and cardiac outputs with exercise were performed on those patients showing minimal alteration of cardiovascular dynamics.

Correlation of the electrocardiographic and radiographic changes with the physiologic and pathologic alterations will be briefly presented. Major emphasis of the paper will be placed on the finding of relatively normal or slightly low cardiac outputs in 15 out of 16 patients.

Cardiovascular Function in Patients with Healed Myocardial Infarction. *Carleton B. Chapman and Robert S. Fraser.** Department of Medicine and the Variety Club Heart Hospital, University of Minnesota, Minneapolis.

The possibility that patients with healed myocardial infarction may have a latent circulatory defect is an important practical point. Those who develop angina pectoris or cardiac failure on recovery from the acute episode must, of necessity, limit their activity; but those who are asymptomatic often are able to resume very active lives. It has often been thought, however, that the activity of such patients should nevertheless be limited. In order to test the validity of this practice, hemodynamic studies were carried out on 9 patients of this type and, for comparison, a group of 12 normal subjects of comparable age was also tested. Cardiac output and mean circulation time were determined by the dye dilution technic before and during (not after) exactly 10 minutes on a treadmill set at 3 mph and 5% grade. Intra-arterial blood pressure recordings were made also during the same phases of the test. There was no statistically significant difference in the mean resting cardiac outputs for the 2 groups (5.71 ± 1.68 L./min. for patients and 6.26 ± 1.77 L./min. for normal subjects). Response of cardiac output to exercise was also similar in both groups (10.38 ± 2.70, and 10.97 ± 1.57 L./min. respectively). This represents an increase in cardiac output of about 1.8 times the resting value in response to exercise of this type. Mean circulation time was within normal limits at rest in both groups, and there was no significant difference between them in the decrease due to exercise. Finally, the degree and sequence of changes in blood pressure during and after exercise failed to differentiate the normal from the abnormal.

It is concluded that although the test used does not determine circulatory capacity, it fails to disclose evidence of circulatory disability at rest or during moderate exertion in the patients as compared with the normal subjects. The results provide no support for the old notion, now mostly discarded, that such patients should be forbidden to indulge in any but the most sedentary activity.

A Method of Controlling Bowel Movements in Patients with Myocardial Infarction. *Robert S. Green and Dominic Davolos.** St. Mary's Hospital, Cincinnati.

The fact of rupture or sudden arrythmia during bowel movements in patients with recent myocardial infarction has been established. The following regime proved valuable in eliminating the need for bowel movements during the critical period of myocardial necrosis: (1) 800 calorie low-residue diet, (2) 5–15 cc. mineral oil every night, (3) careful instruction that the absence of a bowel movement is not harmful.

Twenty-five consecutive patients with recent infarction were studied. The need of a bowel move-

ment from the time of first examination until 3 days after the fever subsided was eliminated in 20 patients. This period ranged from 6 to 16 days. Undesirable side effects, such as cramping or flatus, were minimal. The addition of small amounts of mineral oil every night resulted in a persistently soft stool, so that subsequent bowel activity was easily accomplished, even in patients with previous rectal difficulty.

Failure of the regime was due to patient refusal in 3 instances and to the laxative effect of mineral oil in 2 others. A low tolerance to the laxative effect of mineral oil was noted in patients who were older and of small build.

Studies on the Use of Ethaverine in Angina Pectoris. *David L. Simon* and Arnold Iglauer.* University of Cincinnati College of Medicine, Cincinnati.

Ethaverine, the ethyl analogue of papaverine, was submitted to clinical evaluation in 22 patients with well established angina pectoris from the Cardiac Clinic of the Cincinnati General Hospital.

The patients were observed at weekly intervals and records kept daily on a calendar type card of the number of nitroglycerine tablets used. Doses ranged from 200 to 400 mg. daily in divided dosage.

Following a control period of approximately 6 weeks, either ethaverine or a placebo was administered to each patient for a similar period, following which the patient was given the other material for an additional 6 weeks. Neither the patient nor the physician knew which was being given, and the findings were not evaluated until the study was complete. Modified Master tests were carried out on each patient during each of the 3 periods of the study.

Results: All patients showed a significant improvement over their control periods during the administration of either ethaverine or placebo. However, no statistically significant difference was found between the number of tablets used during the period the patients were on the drug and on the placebo. The Master tests, which were positive in most cases, were uninfluenced by medication. No significant side effects were observed.

An Attempt to Determine the Critical Level of Blood Pressure Necessary to Maintain Glomerular Filtration Rate in Patients with Hypertension by the Use of Ganglionic Blocking Agents for Reducing Blood Pressure. *Warren Hughes,* Robert McConn* and Edward Dennis* (introduced by *John H. Moyer*), Department of Medicine and Pharmacology, Baylor University College of Medicine and the Cardiac Clinic of the Jefferson Davis Hospital, Houston.

With the widespread clinical use of therapeutic agents in the treatment of hypertension, it is desirable to determine a general range of blood pressure reduction to be used clinically which will maintain GFR and avoid impairment of renal function in patients with and without impaired renal function. Patients with hypertension were studied from the standpoint of GFR as related to mean blood pressure reduction when a ganglionic blocking agent (Pendiomide) was used intravenously. GFR was determined by inulin clearance and mean blood pressure was determined by intra-arterial manometry. The mean blood pressure was lowered in a progressive manner approximately 20 mm. Hg at a time until maximum reduction was obtained for 1 hour or more. GFR was determined at each level. Studies showed an initial reduction (average) in GFR which again increased after renal hemodynamic stabilization. When the mean blood pressure was reduced maximally for 1 hour or more, the average mean blood pressure showed a 38% reduction. This represented an average mean blood pressure of approximately 100 mm. Hg, which is well within the normotensive range. At this point the average GFR was reduced about 35%.

It is concluded that in patients with hypertension, when the blood pressure is reduced, there is a decrease of GFR initially, as well as after a period of hemodynamic stabilization which occurs within normotensive levels. There did not appear to be a consistent and predictable blood pressure level at which alterations in GFR occurred.

A Comparison of Results in the Treatment of Hypertension with *Rauwolfia serpentina* Alone and in Combination with Hexamethonium or Hydrallazine. *John H. Moyer, Ralph V. Ford, W. R. Livesay* and Sam I. Miller.** Departments of Medicine and Pharmacology, Baylor University College of Medicine, Houston.

A group of 158 patients with hypertension have been studied on an ambulatory outpatient basis. All patients had an average control blood pressure of not less than 160 systolic and 110 diastolic. Eighty-five of the patients received *Rauwolfia serpentina* (Rauwiloid) alone. Forty-five of the 85 patients were responsive to *Rauwolfia* alone with a fall in mean blood pressure of 20 mm. Hg or more and 19 of these became normotensive with a fall in mean blood pressure to 110 mm. or less. More severe cases and patients with complications due to hypertension were found to be far less responsive than the milder uncomplicated cases. Side effects were all benign. Hydrallazine was added to 11 patients who were unresponsive to *Rauwolfia serpentina* alone, after which 8 became responsive. *Rauwolfia* ameliorated the side effects of hydrallazine and controlled the pulse accelerating action. Four in a group of 9 additional patients who were started on combined *Rauwolfia* and hydrallazine therapy failed to tolerate the latter agent. The remaining 5 responded to treatment. Only 3 patients out of 64 treated with combined hexamethonium and *Rauwolfia serpentina* failed to respond, and 39 of the

responding patients became normotensive in spite of a high incidence of hypertensive complications prior to therapy. Retinopathy was found to be uniformly reversible in 21 cases with this complication. Not only was the hypotensive effectiveness of hexamethonium augmented, but the dose requirement of this agent was reduced and side effects became less intense and more tolerable. No serious side reactions occurred.

It was concluded that *Rauwolfia serpentina* is an effective hypotensive agent in mild uncomplicated hypertension and that a combination of hexamethonium and *Rauwolfia* can be expected to control the majority of severe complicated cases of hypertension. The mild and moderately severe cases of hypertension which do not respond to *Rauwolfia serpentina* alone will frequently obtain a significant reduction in blood pressure when hydrallazine is added to the therapy. However, it is desirable to first treat the patient with *Rauwolfia* in order to block off the untoward reactions which otherwise accompany hydrallazine administration.

Cardiovascular, Cerebral, and Renal Hemodynamic and Metabolic Adjustments to 1-Hydrazinophthalazine in Essential Hypertension. *Charles W. Crumpton, George G. Rowe, Archer P. Crosley, Jr., George M. Maxwell* and John H. Huston.** University Hospitals and University of Wisconsin Medical School, Madison.

Measurements of cardiac output (direct Fick), cerebral hemodynamics and metabolism (nitrous oxide method), and renal hemodynamics and metabolism (right renal vein catheterization) were made in 20 fasting hypertensive patients of Grade II to III severity before and 30 to 60 minutes after intravenous 1-hydrazinophthalazine. Results are expressed in % change from control observations.

Cardiac Output (14 patients—0.20–0.55 mg./Kg.): A significant reduction in MABP occurred (27%) accompanied by a decrease in TPR (41%) and total pulmonary resistance (36%). Cardiac output increased from 6.58 to 8.40 L./min. (28%). Left ventricular work and mean pulmonary artery pressure did not change. Simultaneous *Cerebral Flow and Cardiac Output* (6 patients—0.20–0.25 mg./Kg.): MABP fell 29%. Cardiac output and cerebral blood flow increased 24% and 28% respectively. Total peripheral resistance decreased 38% and cerebral vascular resistance 39%. *Renal Circulation and Metabolism* (6 patients—0.25 mg./Kg.): MABP fell 17%, renal vascular resistance fell 38%, while renal blood flow increased 55%. Oxygen consumption of the body, brain and kidney remained unchanged at the time of significant increases in systemic, cerebral, and renal blood flow. This was accomplished by a rise in oxygen content of the mixed (MPA), internal jugular, and renal venous blood with a corresponding decrease in oxygen extraction. Carbon dioxide content was reduced at the time of the second flow determination. MABP fell as a result of a greater change in TPR (−41%) than in cardiac output (+28%). Systemic, cerebral, and renal blood flow increased at the time MABP was significantly reduced. Systemic, cerebral, and renal vascular resistance decreased proportionately. Changes in systemic and cerebral flow were comparable. Renal blood flow showed the greatest % increase at the time of a smaller change in MABP.

A Syndrome Elicited by Prolonged Administration of Large Doses of Hydrallazine. *Harriet P. Dustan, Robert D. Taylor, A. C. Corcoran and Irvine H. Page.* Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland.

Hydrallazine (600–800 mg. daily) used over long periods (15–30 months) because of sustained amelioration of hypertensive disease has resulted in untoward sequelae in 13 of 139 patients. This is a syndrome which in its milder form resembles early rheumatoid arthritis; and in its severe form, acute systemic lupus erythematosus ("L.E.").

Initial symptoms were arthralgias of fingers, wrists and, less commonly, other joints. Fusiform periarticular swelling of interphalangeal joints simulated rheumatoid arthritis in 8 with the milder form. These showed increased erythrocyte sedimentation rate, serum polysaccharide, alpha and gamma globulin, and decreased serum albumin. One was febrile, anemic and leucopenic. Symptoms abated when hydrallazine was discontinued.

Five patients, either because arthralgia was less or their fortitude greater, continued treatment and developed the severe form with fever (101–104°F.), prostration and anemia. Three had polyserositis; one a severe erythematosus reaction to ultraviolet irradiation, and cutaneous changes resembling "L.E."; one had diffuse, nonspecific "rheumatic" pneumonia. Serum albumin was decreased in all; alpha and gamma globulin fractions were increased. One patient developed a positive plasma "L.E." test; another had "L.E." cells in his bone marrow.

Remission followed withdrawal of hydrallazine in one; symptoms abated in another during treatment. The patient with pneumonia manifestations recovered after drug withdrawal and during administration of isonicotinic acid hydrazide. Two required corticosteroid therapy; one still required maintenance steroidal treatment. Three of 8 patients with milder and 2 with the severe form of the illness have continued hydrallazine in smaller doses.

This illness differs from typical drug hypersensitivity. Academic interest lies in its simulation of acute "L.E."

Effect of Long-term Hydrazinophthalazine-Hexamethonium Therapy on Renal Function in Severe

Essential Vascular Hypertension. *Ivan J. Mader* and Lloyd T. Iseri.* Wayne University College of Medicine, Detroit.

Fourteen cases of severe essential vascular hypertension were treated with progressively increasing doses of parenteral hexamethonium (20–100 mg. per day) and oral hydrazinophthalazine (400–900 mg. per day). All patients were hospitalized and carefully observed at bed rest for at least 2 weeks before drug therapy was instituted, and basal blood pressures were obtained during the last week of observation. Specific renal functions were measured by the clearances of inulin and para-aminohippurate immediately before antihypertensive therapy and again after at least 2 weeks of treatment. Cardiopulmonary hemodynamic studies were done in 4 patients, utilizing the technic of cardiac catheterization. A substantial reduction in blood pressure occurred in 12 patients. RPF increased over 35% in 7 cases, 19 and 21% in 2, showed no significant change in 4, and decreased by 42% in 1. GFR showed no change in 8 patients, increased over 15% in 3, and decreased over 15% in 3. The total renal resistance decreased by 15 to 62% in 12 patients and increased by 14 and 52% in two. The decrease in total renal resistance occurred primarily in the afferent arteriolar system. In the 2 patients who showed an increase in total renal resistance, the changes were found in both afferent and efferent arteriolar resistances. The increase in renal blood flow could not be accounted for by changes in cardiac output in those patients so studied.

These results are interpreted to indicate that long-term hydrazinophthalazine-hexamethonium therapy in severe essential vascular hypertension may improve kidney function.

CENTRAL NERVOUS SYSTEM

Increased Cerebrospinal Fluid Pressure and Papilledema as Independent Manifestations of Malignant Hypertension. *Robert D. Taylor, A. C. Corcoran and Irvine H. Page.* Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland.

Papilledema in hypertensive disease has been attributed to increased cerebrospinal fluid pressure. We have measured cerebrospinal fluid pressure (CSFP) in 100 hypertensive patients without papilledema and in 100 with papilledema. Repeated measurements were made in 20, 90 in 1. Average diastolic blood pressure on the day of observation was associated with CSFP.

Measurements were made in 1 patient during the onset of papilledema, in 1 during its advance from 2 to 4 plus, in 5 during recession of papilledema in response to pyrogen, and in 2 during recurrence.

Normal maximal CSFP was taken as 250 mm. H_2O. CSFP of 87 without papilledema was normal, as it was in 57 with papilledema. There is no constant association between high CSFP and presence of papilledema.

There was no correlation between CSFP and mean diastolic pressure in patients without papilledema. In those with papilledema, the correlation coefficient (r) is 0.347. This is significant since the ratio of r to the standard error of r is 3.5. This association does not establish a causal relationship; thus, mean diastolic pressures of 160 mm. Hg are sometimes associated with CSFP less than 250 mm. H_2O. Onset of, and recession of papilledema could not be associated with changes of diastolic pressure. Variations of CSFP of 50 to 450 mm. H_2O were observed in 1 patient while diastolic pressure was relatively constant.

Increased diastolic pressure per se is not a cause of increased CSFP; increased CSFP is not a cause of papilledema in patients with malignant hypertension. The association suggests they are common but independent sequelae of vascular damage.

COLLAGEN DISEASES—ALLERGY

A Skin Test for Rheumatic Activity in Children: Response to a Nicotinic Acid Ester (Trafuril). *Murray M. Streitfeld and Milton S. Saslaw.* Department of Medical Research, National Children's Cardiac Hospital, Miami, Florida.

Children with active rheumatic fever responded differently from normal, healthy children to the topical application of an ointment containing 5% tetrahydrylfurfuryl ester of nicotinic acid (Trafuril, Ciba), as indicated by a study of 376 children at 6 rheumatic fever institutions.

A "typical" response in normal children consisted of the development of erythema and/or edema at the site of inunction within 30 minutes.

In contrast, 22 of 24 patients with active rheumatic disease gave an "atypical" response, manifested by blanching, or failure to react, or barely perceptible hyperemia. Where the rheumatic disease was inactive or the activity was suppressed by cortisone or aminopyrine, the response was "typical." The type of skin response in rheumatic disease appeared to be directly correlated with changes in the activity status.

Children with congenital heart disease and

other miscellaneous nonrheumatic conditions responded like normal subjects. Those with tonsillitis and streptococcal sore throat gave "atypical" responses.

There were no systemic reactions observed in any case. No significant changes in blood count, sedimentation rate, electrocardiogram or body temperature were demonstrable in the 31 patients in whom such determinations were made.

Inunction with Trafuril may be useful as an aid in the evaluation of rheumatic activity, and further studies to determine its specificity and mechanism of action are in progress.

ENDOCRINES AND METABOLISM

Low Thyroid Reserve: A Clinical Entity. *Luther W. Kelly, Jr.,* Richard P. Levy* and W. McK. Jefferies.* Department of Medicine, Western Reserve University School of Medicine, Cleveland.

The availability of a suitable preparation of thyrotropin (TSH) has led to the development of a test which measures the ability of the thyroid gland to respond to stimulation, i.e., thyroid reserve. It has been demonstrated that a single injection of TSH will produce a significant rise in thyroidal uptake of I^{131} and in serum protein-bound iodine (PBI). This can be measured by comparing the 3-hour thyroidal uptake of I^{131} on successive days and the serum PBI before and 24 hours after the injection of TSH.

Tests have been performed on 96 patients in whom there was a clinical suspicion of hypothyroidism. In 27 individuals the initial I^{131} uptakes were within the normal range, but there was no significant increase following TSH, suggesting low thyroid reserve. Serum PBI determinations confirmed this impression in a number of these patients, but in others there was a normal rise in PBI, indicating that some extraneous factor had interfered with I^{131} response. In some instances exposure to iodine through skin contact or x-ray contrast material was responsible for the apparent discrepancy.

Hence, this test has revealed a type of thyroid abnormality which has not hitherto been clearly recognized. It is characterized by I^{131} uptake and serum PBI in the normal or borderline subnormal range, with a lack of response to TSH stimulation, indicating a remnant of thyroid tissue which is already functioning at a maximum rate and is unable to respond to further stimulation. Such patients present symptoms suggestive of hypothyroidism, but customary tests of thyroid function are normal or equivocal.

Although most instances of low thyroid reserve occur following subtotal thyroidectomy or therapeutic doses of I^{131}, several cases have been observed in whom it occurred spontaneously.

Colorimetric Fractionation of Urinary Ketosteroids in Congenital Adrenal Hyperplasia: The Induction of Qualitative Changes by Treatment with Cortisone and Hydrocortisone. *Edna H. Sobel, Leland C. Clark, Jr.,* Marcia Brussel* and Gwen Prior.** The Fels Research Institute, Yellow Springs, and The Children's Hospital Research Foundation, Cincinnati.

A method is being developed to distinguish among classes of ketonic steroids, based on the fact that the reactivity of the ketone group is related to its position in the steroid nucleus. The procedure was used in studying the neutral lipid extract of acid hydrolysed urine collected from an 11 year old boy who has congenital adrenal hyperplasia with electrolyte imbalance. All results were calculated in terms of dehydroisoandrosterone. It was found that the very high 17-ketosteroid excretion of 112 to 145 mg. per day (Zimmerman) represented only approximately 45% of the total ketonic material excreted (average 290 per day). Twenty-five % of the total was composed of 3- and 20-ketosteroids, while an unidentified group of ketonic compounds ("X") comprised 30% (75 to 120 mg. per day). Oral administration of cortisone acetate or hydrocortisone (100 mg. daily) resulted in reduction of all the steroids measured to about 20% of the control values ($p = 0.004$). Hydrocortisone acetate in the same dose was apparently less effective ($p = 0.028$) as the steroid excretion rose to 40% of the control value. There were distinct qualitative shifts in steroid excretion during treatment with cortisone acetate and hydrocortisone as the 17-ketosteroids (Zimmerman) were reduced to 40% of the total and "X" to 25%, while the relative amount of 3- and 20-ketosteroids increased to 35%. The excretion of "X" rose most rapidly when treatment was discontinued; at the same time there was an episode of moderate dehydration and electrolyte insufficiency. During the immediate post-treatment period "X" was excreted in amounts almost equal to those of the control period, while the other steroids were still somewhat reduced (75% of the control values).

Clinical Results of a Protective Regime During High Dosage Long Term Cortisone Therapy. *Robert R. Commons.* University of Southern California Medical School, Los Angeles County General Hospital and Good Hope Clinic, Los Angeles. (Studies supported by Merck and Co., Schering, The Upjohn Company, G. D. Searle & Co., White Laboratories)

A regime designed to prevent the predictable complications (potassium deficiency, peptic ulceration, osteoporosis, negative nitrogen balance, hypertension, edema, diabetes, masked infections, hypothyroidism, adrenal atrophy, psychoses) of long-term, high-dosage cortisone treatment has been observed during 1 year in 52 of 92 patients. No serious problems have occurred in this group of 52.

Three deaths (tuberculosis, ruptured peptic ulcer, Addisonian crisis) and 3 serious complications (osteoporosis with compression fracture, bleeding duodenal ulcer, congestive heart failure) have occurred in the 40 patients taking similar cortisone dosage without emphasis on protection (usually 50–60 mEq. potassium daily low sodium diet and symptomatic Rx for dyspepsia).

The principles of the protective regime are: (1) hemoglobin, urine sugar, blood iodine and chest film before Rx and repeat each 6 months. Rx if indicated, (2) prompt antibiotics for infection, (3) sodium restriction to 500 mg. daily, (4) frequent feeding high protein diet, (5) at least 100 mEq. potassium supplement daily, (6) full dosage atropine or other anticholinergic, (7) androgen and/or estrogen.

The patients treated had suffered from severe allergic or inflammatory diseases refractory to other modes of therapy. These diseases responded to cortisone as expected. Facial mooning, acne, hirsutism were valuable clinical guides to indicate adequate suppressive doses of cortisone.

The Consistency of Urinary Gonadotropin Levels in Castrate Women, and Their Time Relationships to Estrogen Therapy. *R. Palmer Howard, Corinne Keaty* and Edward C. Reifenstein, Jr.* Oklahoma Medical Research Foundation, Oklahoma City.

Urinary titers of gonadotropins (FSH) were determined by the method of Klinefelter, Albright and Griswold on 100 specimens from each of 2 castrate women. The patients received several courses of an oral preparation of equine conjugated estrogens (Premarin). 10 mg. daily proved necessary for prompt and consistent reduction of the urinary gonadotropin levels.

The control levels of urinary gonadotropins usually were >384 <768 m.u./day or higher. However, the titer was >192 <384 mU/day in 3 out of 44 assays. After the effect of estrogen therapy was fully manifest, levels >96 <192 mU/day or lower were noted except for 3 assaying >192 <384 mU/day out of the total of 42 specimens.

In 5 courses of therapy the time required for significant reduction of the urinary gonadotropin level was consistently between 8 and 12 days. However, the time required for the return to the pretreatment level after cessation of therapy differed in the 2 patients; 9–12 days on 2 occasions in the first, 17–26 days on 2 occasions in the other.

Appreciation of the degree of consistency in the gonadotropin levels, and knowledge of the time relationships between the initiation or cessation of therapy and these levels, are necessary for the proper application of this method in determining the potency of estrogenic substances in castrate women.

Depression of Gonadotropin Excretion as a Method for the Assay of Estrogens in the Human Subject. *Robert B. Leach,* Ichiro Tokuyama,* C. Alvin Paulsen and William O. Maddock.* Wayne University College of Medicine, Detroit.

Several clinical methods for assaying estrogens have been devised in which criteria such as alleviation of menopausal symptoms or induction of "withdrawal bleeding" have been used for comparing estrogenic potency. Each of these procedures, however, has definite shortcomings, and the need remains for methods which are objective and accurate and can be performed in readily available subjects.

Therefore, the ability of estrogens to decrease urinary gonadotropin excretion was studied in 21 postmenopausal or castrated women to determine if this property would afford a useful method for comparing estrogens in the human subject. The ovarian weight of immature female rats was used to determine urinary gonadotropin levels. Assays were performed before, and at approximately 1-month intervals during therapy. Five oral estrogen preparations were studied: diethylstilbestrol, conjugated estrogens equine (Premarin), potassium estrone sulfate, estradiol., and potassium estradiol sulfate. Relatively small changes in estrogen dosage produced clear-cut differences in gonadotropin excretion. Whereas 0.5 mg. diethylstilbestrol daily produced a significant decrease in gonadotropin excretion in only 1 of 6 patients, 1.0 mg. produced definite suppression in each of 7 patients. Conjugated estrogens equine was ½, potassium estrone sulfate was ¼, and estradiol and potassium estradiol sulfate were ⅛, as potent as diethylstilbestrol.

It is concluded that the determination of the minimal amount of estrogen necessary to decrease the urinary gonadotropin excretion of postmenopausal or castrated women affords a method for comparing the potency of estrogens, which is accurate and objective and can be performed in readily available subjects.

Observations on Menopause Symptoms as Related to Hypoglycemia Phenomena Reproducible by the 6-Hour Dextrose Tolerance Test, Partly Controllable with Insulin Hypoglycemia Treatment and Proteins. *Herbert A. Weitzner.* Department of Internal Medicine, Kaiser Foundation Hospital, Oakland, California (Insulin, in part, supplied by E. R. Squibb & Sons)

Concurrent with other studies it was noted

that many menopause symptoms (flushing, chilling, nervousness, sweats, irritability, exhaustability, tremor, emotional outbursts, headaches, fitful sleep, dizziness, palpitations, etc.) resembled the symptoms reproduced by hypoglycemia during the 6-hour dextrose tolerance test or by prolonged mild insulin-induced hypoglycemia.

Similar studies were therefore made on 50 women, taken at random, aged 45–60 who had typical menopause symptoms from 2–15 years, some partially dependent upon estrogens and/or androgens for relief. No patient was briefed prior to the dextrose test or to the insulin reactions. During subsequent interrogations, 92% of patients identified many of their menopause complaints with their experiences following dextrose or insulin hypoglycemia. 8% were noncomittal.

Treatment consisted of 2 consecutive phases: (1) mild hypoglycemia induced by insulin, terminated 1¼–1½ hours postinjection (tremors, sweat, hunger), 3 times weekly as described elsewhere (Permanente Foundation Medical Bulletin, *X:* 112, 1952), and (2) increased protein intake (1¼–1½ lb.) every 2–3 hours and decreased carbohydrates especially during the first 8 hours of the day (to lessen the "Staub-Traugott effect") and no carbohydrates at the evening meal. These measures eliminated most menopause symptoms in 92% of the patients.

Ninety-two per cent of the patients demonstrated increased sensitivity to insulin in which decreasing amounts produced the identical reactions, possibly due to healthier liver activity as reflected in an improved dextrose tolerance curve (less "diabetic"). Hypoglycemia symptoms increased in many patients, suggesting a carbohydrate influence upon the liver.

After controlled treatment with insulin hypoglycemia, many menopause symptoms in 46 of 50 patients were lessened or eliminated by increased proteins and decreased carbohydrates.

Speculatively, other hormones may exert an elevating or "buffering" effect upon the blood sugar as part of treatment in menopause.

Symptoms of "Spontaneous Hypoglycemia" and "Hyperinsulinism" Commonly Encountered: Routine Use of 6-Hour Dextrose Tolerance Test as a Valuable Diagnostic and Clinical Tool. *Herbert A. Weitzner.* Department of Internal Medicine, Kaiser Foundation Hospital, Oakland, California.

Of 400 patients, 200 were given the 2–3-hour and 200 the 6-hour dextrose tolerance tests. No symptoms occurred under 2 hours, a few under 3 hours, and most between 3–6 hours. Blood glucose ranged from: fasting of 85–160 mg./%, postdextrose hyperglycemia 120–360, and hypoglycemia 55–95. 99% of the 6-hour patients noted some or most of the following symptoms in sequence from 2–6 hours: confusion, drowsiness, restlessness, poor concentration, blurred vision, headache, weakness, uncertain gait, irresistible sleepiness, hunger, nausea, flushing, chilling, tremor, perspiration, anxiety, irritability, garbled speech, scotomata, disordered depth and time perspective, impaired judgment, emotional outbursts, muscle cramps, chest pain, hyperventilation, throat constriction, palpitation, occasional syncope and partial amnesia. Most symptoms were reversed by food.

Symptoms following dextrose were strikingly similar to those reported in hyperinsulinism and spontaneous hypoglycemia, yet none of our patients had organic endocrinopathy or liver disease. Our patients identified some dextrose-test symptoms with their complaints, for which medical and psychiatric aid had occasionally been requested.

Routine 6-hour dextrose tolerance tests (100 Gm. orally) upon 200 patients (organic and functional) indicated that hypoglycemia symptoms were: (a) almost universal, (b) normal, (c) distressing, (d) not necessarily indicative of organic or psychiatric disorders, (e) almost life-long patterns, (f) normal reactions to food, (g) counterparts to a physiologically necessary hypoglycemia.

Normally, hypoglycemia produces adrenocortical secretions via the hypothalamus-pituitary, and therefore cannot be regarded as a disease. The symptoms, however, may distress the individual in regard to his family, automobile driving, factory work, army duties, climacteric, etc. Hence symptomatic treatment is indicated.

Tension-Like (Vascular, Migraine) Headaches Produced by 6-Hour Dextrose Tolerance Test and Insulin Hypoglycemia: Possible Control by Mild Insulin Hypoglycemia and Food. *Herbert A. Weitzner.* Department of Internal Medicine, Kaiser Hospitals, Oakland, California. (Insulin, in part, supplied by E. R. Squibb & Sons, Depo-Testosterone Cyclopentylpropionate supplied by Upjohn.)

Tension-like (vascular, migraine) headaches were noted in 100 Gm. dextrose tolerance testing of 400 patients, divided into similar groups: "A" for 2–3 hours, "B" for 6 hours.

Ten per cent of "A" developed mild headaches (15% in migraine patients) which disappeared after eating, while 90% of "B" developed mild to severe headaches (96% in migraine patients), 50% persisting 12–24 hours following food. Retesting some patients in reversed groupings gave unchanged results.

These hypoglycemia headaches were indistinguishable by the patients and observer from tension headaches—spread from one focus, throbbing, expanding, bursting, intolerable pain with frequent scotomata, anorexia, photophobia, somnolence and

irritability. Headaches increased directly with: (1) total blood sugar drop from high to low points, (2) increased time intervals between high and low points, (3) depressed rise from low point to fasting level (gluconeogenesis and glycogenolysis).

Treatment with aqueous insulin hypoglycemia (tremor, perspiration, hunger) 3 times weekly, under 1¼ hours produced no headache. Headache increased with: (1) reaction time beyond 1¼ hours, (2) vague hypoglycemia reactions, (3) insufficient food to prevent endogenous reactions, (4) carbohydrates, (5) proteins below ¼ pound every 1½ hours on insulin days.

During treatment, 90% of 200 patients' sensitivity to insulin and dextrose demonstrated a "more tolerant" dextrose test without developing severe headaches.

Headaches were lessened or prevented between treatments by proteins or ergotamine tartrate. In some, testosterone (Upjohn, Depo) or estrogens reduced the intensity, but did not prevent the headaches.

Tentatively, tension-like (vascular, migraine) headaches studied by dextrose or insulin hypoglycemia may be reproduced and possibly prevented by treatment with controlled insulin hypoglycemia and food.

Sleep Paralysis Controlled with Insulin Hypoglycemia. *Herbert A. Weitzner.* Department of Internal Medicine, Kaiser Foundation Hospital, Oakland, California.

This observer noted that insulin-induced hypoglycemia restored normal sleep in rheumatoid arthritis patients, possibly via the hypothalamus. These experiences were applied to the study of sleep paralysis, a disturbance in awakening from sleep wherein a prolonged delay exists between sensory and motor response. Two patients were successfully treated with mild insulin-induced hypoglycemia. One of them, E. T., was reported in detail elsewhere (Arch. Neurol. & Psychiat., *68:* 835, 1952). Both were of progressive severity, thus permitting detailed studies. The neurologists and psychiatrists of the hospital had declared both patients to be normal.

E. T. had as many as 28 attacks of sleep paralysis per week, and only once within 5 years went for 1 week without any attack. As of October 8, 1951, when first treated with insulin, he has been free from sleep paralysis, except upon 1 occasion of an accidentally prolonged hypoglycemia. Treatment was discontinued since October 12, 1952, with no recurrences to date.

A second patient, R. P., suffered up to 20 attacks of sleep paralysis each week, as well as cataplexy and narcolepsy for over 15 years. The maximum time without any sleep paralysis was 1 week. Treatment with insulin-induced hypoglycemia was begun December 1, 1952. He has had but 2 brief recurrences of sleep paralysis to date, although his treatment was discontinued May 1, 1953.

Two patients with frequent attacks of sleep paralysis underwent immediate and almost continuous remissions following the first treatment of mild insulin-induced hypoglycemia of short duration. Remissions have persisted upon cessation of treatment. Total remissions since onset of treatment have been 24 and 9 months respectively.

Skin Test Responses to Insulin and Serum Antihormonal Activity in a Case of Combined Insulin Allergy and Resistance. *Samuel C. Bukantz* and William G. Klingberg* (introduced by *Robert J. Glaser*). The Department of Medicine and the Department of Pediatrics, Washington University School of Medicine, St. Louis. (Insulin supplied by the Eli Lilly Company)

A 3½ year old male diabetic child was admitted to the St. Louis Children's Hospital in moderate acidosis. Controlled with 12 units of regular and 6 units of protamine zinc insulin prior to his admission, he exhibited considerable insulin resistance during hospitalization and could not be regulated with 350–430 units of regular insulin daily. Concurrently he exhibited marked local reactions at injection sites, conjunctival reddening and nasal congestion following injections and a blood eosinophilia of 17%.

Direct intradermal skin tests were performed with .02 ml. of a number of insulin preparations. Beef, pork, and mixed crystalline insulins provoked wheal and erythema reactions, while control normal and nonallergic diabetic subjects yielded no reactions. Because positive skin tests were also obtained with beef, but not with pork muscle extract, it seemed evident that the patient was reacting to the insulin preparations.

Aged neutralized commercial insulin yielded a positive skin test while trypsin digested insulin (free of hyperglycemic factor) yielded negative skin tests. A solution of hyperglycemic factor, alone, at 25 γ/cc. concentration, yielded a positive skin test comparable to that of crystalline insulin. Exposure of commercial insulin to boiling water for 30 to 180 minutes had no effect upon the skin reactive material. Treatment of the child with trypsin digested insulin for 24 hours had no greater effect on reducing blood sugar than had commercial insulin.

Serum from the patient and control subjects exhibited antihormonal properties in mouse convulsion tests.

The observations suggest that: (1) allergy to insulin was directed against a contaminant rather than the hormone, (2) the allergen in insulin is heat-stable, and (3) serum from normal, as well as diabetic patients may exhibit anti-insulin properties in mouse convulsion tests.

The Effect of Carbohydrate Deprivation on the Metabolism of Fructose and Glucose in Normal Subjects. *James W. Craig, Max Miller and Hiram Woodward, Jr.** Cleveland.

Starvation has long been known to produce an alteration in the ability of the organism to handle exogenous carbohydrate ("starvation diabetes"). The location of the metabolic defect responsible is not definitely known, although recently it has been suggested that pituitary respiratory-quotient depressing factor is formed, which inhibits the transformation of hexosediphosphate into pyruvate. This would imply that the metabolism of both fructose and glucose would be impaired, since fructose enters the metabolic scheme before the hexosediphosphate step.

Intravenous glucose and fructose tolerance tests (1 Gm./Kg./hr.) were performed in each of 4 human volunteers before and after 2 days of complete starvation or 2 days of a high protein, carbohydrate-free diet. The glucose disappearance curves were abnormally elevated in every instance after carbohydrate deprivation. In contrast, the fructose disappearance curves were unaltered. After carbohydrate depletion, in 3 of the 4 cases, the blood pyruvate rise was less after glucose administration, while in 3 of 4 cases fructose resulted in a greater pyruvate rise.

The finding that the handling of fructose is not impaired after starvation would militate against the hypothesis that there is a block after hexosediphosphate. Rather, it suggests that the block may be primarily at the glucokinase step, similar to that found in diabetes mellitus and in the loss of tolerance to glucose found in the "alarm reaction."

Ionic Interrelationships and Potassium Intoxication. *W. H. Meroney and R. F. Herndon.** Army Medical Service Graduate School, Washington, D. C.

Thirty-two patients with post-traumatic renal insufficiency were examined for interrelationships of potassium, inorganic phosphate, calcium, sodium, and the electrocardiogram. The nature of the preceding trauma and associated circumstances, in the combat zone of Korea, resulted in an early rise of plasma potassium to toxic levels. In all cases the hyperkalemia was asymptomatic until it progressed to the point of imminent ventricular fibrillation. The degree of hyperkalemia was reflected quite accurately by the electrocardiogram in those instances where the plasma phosphate was normal.

The influence of hyperphosphatemia was mediated through the inverse relationship of phosphate with calcium during oliguria. As phosphate rose, calcium fell predictably. Calcium is a specific antagonist of potassium, and the calcium deficit provoked by the phosphate excess diminished the normal opposition to potassium, allowing a given potassium excess to exaggerate the electrocardiographic evidence of intoxication to a degree comparable with a greater potassium excess associated with a normal calcium level.

Replacement of the calcium deficit caused immediate and striking modification of the electrocardiogram without affecting the measurable plasma level of potassium.

Plasma sodium tended to be low in these patients, and raising the sodium levels caused the potassium levels to fall. The effects of the anions combined with sodium, and the dilution of the plasma by the infusions, could be ruled out as causes for the changes.

Studies in Magnesium Metabolism. I. Serum Magnesium in Health and Disease. *H. H. Jones, Jr. and L. D. Bunch.** Sponsored by the H. L. Snyder Memorial Research Foundation, Winfield, Kansas.

Eight hundred and fifty serum Mg levels were determined (method of Orange and Rhein, J. Biol. Chem. *189:* 379, 1951) on 293 miscellaneous medical and surgical patients. 52 analyses were done on 35 healthy controls. A mean of 2.02 mg./100 ml. (S.D. ± 0.176) was found for the control group. Serum Mg values falling outside the range of 3 standard deviations were considered to be probably abnormal.

Values in 8 of 10 patients with hypertensive cardiovascular diseases were found to be abnormally high. Of 16 alcoholics studied, 9 had Mg levels below normal, 2 above normal, and 5 within normal limits. There was no connection between Mg concentration and delirium tremens or malnutrition. Eight patients with infectious hepatatis showed no deviation. In 28 patients with miscellaneous febrile infectious diseases, only 9 showed aberrations. The group as a whole showed no relationship between clinical condition and serum Mg. Of 36 multiple sclerosis patients, 2 had low values—one patient was seriously debilitated, the other was normally active. 17 major surgical patients showed wide swings in serial determinations but no consistent pattern was evident.

This study revealed no correlation between serum Mg and serum Fe or K values.

The most striking deviations from normal in serum Mg values were noted in the hypertensive and alcoholic groups. There were no clinical patterns associated with the observed Mg aberrations. It is probable that balance studies will be required to define the role of Mg in health and disease.

GASTROINTESTINAL SYSTEM

The Effect of Eating Upon the Absorption of Vitamin A. *Albert I. Mendeloff.* Nutrition Research Laboratory, Department of Preventive Medicine, Washington University School of Medicine, and the Barnes Hospital, St. Louis.

The absorption of vitamin A in oily solution, given orally to subjects in the fasting state, has been generally accepted as a measure of fat absorption. When a test dose of 100,000 μg. of vitamin A palmitate was administered in this manner to 16 apparently healthy subjects, the serum vitamin A levels of 5 subjects failed to rise appreciably during a 6-hour period. In these same 5 subjects, ingestion of food 2 hours after administration of the test dose produced a rapid rise in the serum concentration of vitamin A.

When this same test dose was administered to 48 fasting hospitalized subjects, ingestion of food 2 hours later produced in all a marked acceleration of the rate at which the serum vitamin A concentration had been rising. These findings prompted a study of the possible roles of the stomach and small intestine in vitamin A absorption, as follows:

1. Three totally gastrectomized subjects showed the same response to eating as did the normal subjects.

2. Three normal subjects demonstrated the same response to sham feeding as to actual ingestion of food.

3. Six normal fasting subjects received vitamin A intraduodenally, with little evidence of absorption in the following 4 hours. When the test was repeated, ingestion of food was followed by the expected rise in serum vitamin A levels. This effect of eating could not be blocked by parenterally-administered atropine.

4. In two subjects, 12 inches of upper jejunum were "isolated" by inflated recording balloons, and vitamin A was instilled into the isolated loop. No absorption could be detected until after the subjects took food by mouth.

5. Thirteen patients with steatorrhea due to various causes failed to absorb the test dose even after eating.

The significance of these results is discussed, and a new procedure for the vitamin A tolerance test is described.

Microscopic Study of the Human Gastric Mucosa in Vivo. *Ronald K. Doig and Stewart Wolf.* University of Oklahoma School of Medicine, Oklahoma City.

A microscopic study of the human gastric mucosa in vivo is reported for the first time. The units seen correspond to the earlier anatomic studies of Mall on animals, and consist of venous lakes separated by glandular stroma. An enormous variation in size of the vascular structure was noted which corresponded roughly to the degree of prevailing secretory activity in the stomach. Under some circumstances it was possible to identify a deeper vessel which bled intermittently in response to local trauma. The response of the mucosa to locally applied pharmacodynamic agents, and the course of events following trauma, are described.

INFECTIOUS DISEASES—ANTIBIOTICS

Latent Viral Infections of Cells: An Experimental Approach. *J. Donald Hare* and Herbert R. Morgan.* Rochester, New York.

The ability of a number of viruses to remain dormant in host tissues for long periods without causing a manifest disease state is well recognized, as in the latent infections or carrier states seen in human infections with herpes and psittacosis viruses, which permit survival of virus in a population for long periods and also may account for the recrudescence of herpes simplex infections in man or psittacosis in birds. The nature of this alteration of host-parasite balance which results in recurrent disease is poorly understood.

An experimental approach to the problem of virus latency is presented here, using psittacosis virus. The growth of this virus was studied in cultures of tissues which, when maintained in a nutritionally deficient medium alone, lost their ability to support the growth of virus. The addition of beef embryo extract (BEE) to these cells restored this ability.

The enhancement of virus multiplication by BEE took place not only in cultures infected early, but also in cultures made deficient prior to infection. In the latter case, virus could remain in tissues for up to 5 days, with no multiplication, and still be induced to propagate.

It has been possible to show that the factors present in BEE responsible for this action are dialyzable, and that the action does not depend entirely on a new population of cells. A chemically defined medium will duplicate the action of BEE. The implications of this study with reference to viral infections are discussed.

The Induction of Myocardial Lesions by a Coxsackie (Pleurodynia) Virus and Cortisone. *Edwin D. Kilbourne,* Dorothy Perrier* and Charles Wilson.** Department of Medicine, Tulane University of Louisiana, New Orleans.

Coxsackie viruses are defined by their predilection for infant mice and hamsters, and their inability to induce fatal disease in adults of these species. It has been demonstrated (Kilbourne and Horsfall, 1951) that the administration of cortisone to the adult mouse changes this state of intrinsic resistance to one of marked susceptibility terminating in death.

In the present investigation efforts have been made to adapt a strain of Coxsackie virus to the adult mouse by serial passage in the cortisone-injected host. The virus employed (tentatively classified as a Dalldorf Group B strain) was recovered directly in cortisone-injected adult mice from the stool of a patient with epidemic pleurodynia. Viral passages have been effected by the intraperitoneal inoculation of 10^{-2} brain suspensions in CFW mice concomitantly injected with 5 mg. of cortisone acetate. On the 11th passage gross necrotic lesions of the myocardium were discovered by chance. Subsequent investigation of this phenomenon has adduced the following information:

1. Lesions are associated with the presence of virus in the myocardium.

2. Lesions are prevented by specific viral antiserum.

3. Cortisone is a requisite for the induction of gross lesions, but microscopically discernible myocarditis may occur in later passages with virus alone.

4. Repetition of the initial and 4th viral passages with cortisone resulted in microscopically but not grossly evident myocarditis. It is thus probable that a degree of viral adaptation to the cortisone-injected adult has been accomplished by passage.

These experiments demonstrate that a hormone-viral synergism may be effected to induce devastating pathologic change in a "resistant" host.

KIDNEY AND URINARY TRACT

Studies of the Dynamics and Chemical Anatomy of Cyst Fluid in Cystic Disease of the Kidneys. *Neal S. Bricker and John F. Patton.** Research and Development Branch and the Urology Section, Surgical Service, Fitzsimons Army Hospital, and the Departments of Medicine and Urology, University of Colorado School of Medicine, Denver.

Do cystic nephrons in polycystic kidneys serve as functional units? The present studies, undertaken to explore this possibility, were performed at the time of surgical exposure of 6 polycystic kidneys (4 adult patients and 1 infant), and 3 kidneys with solitary cysts (adult). Cyst fluid (CF) was sampled before and at timed intervals following IV injection of inulin and PAH.

In all adult polycystic kidneys, following inulin injection, the inulin concentration of CF exceeded preinjection levels in the majority of cysts sampled. In the infant kidney, however, inulin appeared in increased concentrations in only 3 of 11 cysts. It does not seem likely that entrance of inulin into CF can be explained by diffusion alone, since no gross change in inulin concentration occurred in any of the solitary cysts, nor even in 5 small daughter cysts adjoining a solitary cyst. In polycystic kidneys, PAH appeared to enter the same cysts as did inulin.

Concentrations of creatinine in CF from polycystic kidneys varied widely, but roughly corresponded to the cyst sites. Thus, the CF/Plasma ratio (CF/P) approximated 1 in 65% of superficial cysts, and ranged from 3 to 43.2 in 73% of deep cysts. CF/P did not exceed 1 in the solitary cysts.

Both Na and total solute concentrations in CF frequently exceeded plasma levels. Occasional very low Na values were found.

The possibility of functional activity of cystic nephrons is discussed on the basis of the foregoing data.

The Hemodynamic, Metabolic, and Electrolyte Responses of the Human Hypertensive Kidney to the Intravenous Administration of Sodium p-Sulfamyl Benzoate. *Archer P. Crosley, Jr., George G. Rowe and Charles W. Crumpton.* University Hospitals, Madison, Wisconsin.

This study was performed on 7 fasting hypertensive patients utilizing standard clearance technics and right renal vein catheterization before and after the intravenous administration of 2 Gm. sodium p-sulfamyl benzoate.

Within 15 minutes, and persisting for the 60 minutes of observation following the injection of this agent, statistically significant increases in the clearances of sodium (+160–2200%) and C_{Na}/C_I ratios (+185–2700%) were noted in all patients. These were associated with significant enhancement of urinary pH, clearances of potassium and C_K/C_I ratios. In one patient, the latter ratio equaled 1.34. Chloride clearances and ratios showed greater variability, increasing in 4, decreasing in 2, and associated with no change in an additional patient.

Despite these marked alterations in electrolyte excretion no significant changes were noted in mean arterial blood pressure, urine flow renal hemodynamics, or renal oxygen consumption (calculated as the product of total renal blood flow and arteriorenal venous oxygen difference). Simultaneous

studies of cardiac output (direct Fick) in 5 patients showed changes varying from +24 to −37%.

These results demonstrate the ability of sodium p-sulfamyl benzoate to enhance the excretions of sodium and potassium by a specific blockade of renal tubular carbonic-anhydrase systems. In addition, these marked alterations, coupled with an unchanged renal oxygen consumption, fortify the concept that renal oxygen utilization is primarily directed toward the maintenance of the functional integrity of the kidney, and to a much lesser extent towards the performance of external work.

The Maximal Renal Tubular Reabsorption of Fructose in Normal and Diabetic Man. *Walter M. Kirkendall,* David W. Sinton* and James W. Culbertson.* State University of Iowa, Department of Internal Medicine, Iowa City.

The maximal tubular reabsorption of fructose (Tm_f) by the kidney has not been satisfactorily demonstrated in man. Using arterial blood samples, relatively stationary plasma fructose levels and sodium thiosulfate as the measure of glomerular filtration rate, we attempted to find this value. We gave hypertonic solutions of fructose to 5 diabetic patients, and to 7 other persons without significant disturbance of their carbohydrate regulating mechanism or kidneys. In most subjects plasma glucose levels steadily rose during infusion of fructose, reaching values of 240–357 mg. % glucose in the diabetics (none of whom had insulin for 12–24 hours).

The reabsorption of fructose varied from 38–130 mg./min./1.73 M^2 of body surface area in normals and 40–104 mg./min. in diabetics. Except for 2 normals who had 26 and 81% rises in fructose reabsorption as the serum fructose levels rose from 130 to 385 and 200 to 675 mg. %, respectively, there was no significant rise in reabsorption of fructose above plasma levels of 60 mg. %.

We conclude that the Tm_f in man varies from 40 to 130 mg./min. Saturation of all tubular reabsorptive mechanisms probably occurs at serum fructose levels under 100 mg. % in most normal persons. Diabetics have Tm_f values similar to normal persons, and these are not altered at increased plasma glucose levels. Fructose is a potent osmotic diuretic at high plasma levels. At 675 mg. % plasma fructose, 1 normal had a urine flow of 36.7 ml./min.

The Renal Excretion of I^{131}: Simultaneous Determinations of I^{131} and Inulin Clearances in Varying States of Thyroid and Renal Function. *Neal S. Bricker and Charles J. Hlad, Jr.** The Research and Development Branch, Fitzsimons Army Hospital; the Radioisotope Unit, Veterans Administration Hospital; and the Departments of Medicine and Physiology, University of Colorado School of Medicine, Denver.

The present study represents an attempt to define basic physiologic processes involved in the renal excretion of I^{131} in varying states of renal and thyroid function. Although the rate of renal excretion of I^{131} has been widely investigated, little information is available regarding the fundamental processes of renal iodide excretion. Previous measurements of I^{131} clearance (C_I^{131}) have been performed using single injection technics without apparent surface area corrections, and values do not appear to have been related to other renal functions.

C_I^{131} has been measured simultaneously with inulin clearance (C_{in}) using standard continuous infusion technics. A calculated tracer dose of I^{131} was administered intravenously in the inulin-PAH priming solution, and plasma levels were maintained by constant infusion of an I^{131}-inulin-PAH sustaining solution. Na, K, and Cl were measured in plasma and urine.

C_I^{131} was roughly proportional to C_{in} in all groups studied despite a wide range of filtration rates; the higher C_I^{131} values corresponded to the higher glomerular filtration rates and the lower I^{131} clearances to the lower filtration rates.

Comparison of percentage filtered load excreted (C_I^{131}/C_{in}) with C_{in} revealed a decreasing C_I^{131}/C_{in} with an increasing C_{in}. This suggests a regulatory role of the kidney with respect to iodine economy.

Theoretic concepts of the role of the renal tubules in the excretion of inorganic iodide are examined in the light of the foregoing data and in relationship to the renal excretion of other electrolytes.

LIVER AND BILIARY TRACT

The Use of Scintography for the Diagnosis of Liver and Gall Bladder Disease. *Lloyd A. Stirrett and Eric T. Yuhl.* Surgical Service and Radioisotope Unit, Veterans Administration Center, and the Departments of Surgery and Radiology, School of Medicine, University of California, Los Angeles.

New radioisotope tracer technics have been developed for the diagnosis of liver and biliary tract disease. A scintillation counter and scanning device (the scintiscanner) are employed to record the concentration of radioactivity present within the liver and gall bladder.

For the determination of gall bladder function, 300 μc. of radioactive di-iodofluorescein (I^{131}) is administered intravenously. Thirty minutes after

injection of the tracer agent, the patient is positioned under the scintiscanner and the gall bladder area is scanned. The concentration of the radiodye within the gall bladder is recorded on the scintigram. The procedure is completed in 20 minutes, is free of any toxic reactions and is of particular value where the patients condition precludes the use of orally administered contrast media. A high degree of accuracy has been obtained in a series of over 70 patients with gall bladder disease.

Scintigrams of the liver have been obtained using radioactive colloidal gold (Au^{198}) as the tracer agent. Due to the high degree of affinity of the von Kupffer cells for colloid matter the radiogold is rapidly concentrated within the liver parenchyma. The distribution of the radioactivity is recorded by the scintiscanner. Areas of liver parenchyma which have been replaced by neoplasm or abscess are visually delineated on the scintigram and appear as foci of diminished radioactivity. The technic has been successfully used for the diagnosis of liver neoplasm in a series of 35 patients.

The Significance of Hepatic Hemosiderosis in Patients with Liver Disease. *H. J. Zimmermann, Morton H. Koulish* and Clarence McWhorter.** V. A. Hospitals, Omaha and Chicago (West Side); University of Nebraska and University of Illinois College of Medicine.

It is well known that increased amounts of hemosiderin can be demonstrated in the hepatic cells of some patients with cirrhosis of the liver. A variety of hemochromatosis (cytosiderosis) in animals and in humans has been related to dietary insufficiency. In an attempt to clarify the relationship between cirrhosis with increased pigment deposition and hemochromatosis, the hemosiderin content of 135 consecutive specimens of liver tissue obtained at needle biopsy was studied. In 45 of these the histologic diagnosis was cirrhosis, in 14 fatty metamorphosis, in 10 hepatitis, and in 43 there was no demonstrable hepatic disease. Sections were stained with the Turnbull blue stain for iron. In 36% of the patients with Laennec's cirrhosis there were distinctly increased amounts of pigment which gave a positive staining reaction for iron while only 18%, 15% and 8% of patients with hepatitis, fatty livers or postnecrotic cirrhosis, respectively, showed increased hemosiderin deposits. In only three of 43 patients without hepatic disease was there a demonstrable iron pigment. One of these had "transfusion siderosis," while the other 2 were severe alcoholics. In 2 patients studied serially, there seemed to be a relationship between the changing severity of the liver disease and of the intensity of hepatic hemosiderosis.

The factors related to and the implications of these results are discussed.

Alterations in Serum Diastase and Albumin Values in Protein Deficiency. *James F. Sullivan* and William A. Knight, Jr.* St. Louis.

Nutritional deficiencies, particularly protein deficiencies in animals, are known to produce degeneration of the acinar tissues of the pancreas and fatty infiltration of the liver.

Because of these experimental findings, patients admitted to the hospital with evidence of malnutrition were studied for changes in the serum proteins, pancreatic and hepatic functions. In 6 cases studied there has been a definite correlation between the serum diastase and albumin values. Initially low diastase and albumin levels showed progressive increase with clinical improvement.

The cases presented bring up for discussion several important problems in the field of pancreatic disease.

Choline Deficient Diet, Cirrhosis and Hepatoma. *Michele Gerundo.* Department of Pathology, Creighton University Medical School and Department of Medical Services, Guam, M. I.

The study was carried out by varying the amounts of proteins, carbohydrates and fats. One group of 1-month old Sprague-Dawley rats was kept for 2 months on a choline deficient diet before p-dimethylaminoazobenzene was added to the diet. For another group of 10-month old rats deficient diet and dye were begun at the same time. The experiments were continued for 10 months and animals from each group were sacrificed from time to time to observe progressive changes.

From comparison with controls the following conclusions can be drawn at this time: (1) In choline deficiency p-dimethylaminoazobenzene may act as methyl group donor and retard or prevent cirrhosis. (2) Animals receiving 20% casein showed no ill effects and developed no tumors. (3) Animals on a 30% carbohydrate diet and only 10% casein showed extensive cirrhosis, but no tumors. (4) Animals on a 30% fat diet showed formation of cell clusters or nodules with hyperchromatic nuclei and amitotic figures. No cirrhotic changes were seen, except near the nodules where fibroblasts were proliferating as to encircle and separate them from the rest of the parenchyma. In several animals of this series blood vessel tumors were found in the lungs. (5) Cirrhosis is not a precursor of hepatoma, but fibrotic changes follow formation of atypical cell clusters either as direct stimulus by the cells or as a defense mechanism. (6) Administration of the dye is not the only important factor in the development of hepatoma. Diet, age, sex and other metabolic factors must be considered.

METHODS

The Clinical Application of Filter Paper Electrophoresis. *H. J. Zimmerman, F. L. Humoller* and P. Heller.* V. A. Hospitals, Omaha and Chicago (West Side).

In the past electrophoresis has been too expensive and time-consuming to warrant extensive clinical application. The recent development of filter paper electrophoresis has provided a sufficiently simple and inexpensive clinical tool for the study of proteins in the serum and other body fluids.

The procedure is performed in a barbital buffer at a pH of 8.6 and an ionic strength of 0.05. Only 0.01 or 0.005 ml. of serum need be used. This may be obtained from venous blood or by use of a capillary tube for drawing and centrifuging of fingertip blood. The patterns obtained were analyzed by staining the paper and cutting the strips into three sections corresponding to: (1) the albumin fraction, (2) the gamma globulin fraction, and (3) the residual globulin fractions which included the alpha 1 and 2 and beta globulins. The dye was then eluted for quantitative determination of each fraction. Sera from 30 normal and 300 patients with miscellaneous diseases have been studied. The values obtained on the normals agree with those published by others. Elevation of the gamma globulin levels was found in patients with Laennec's and postnecrotic cirrhosis, rheumatoid arthritis and rheumatic fever, chronic suppurative disease, subacute bacterial endocarditis, lymphomas and bronchogenic carcinomas. Abnormally low levels of this protein fraction were found in hyperadrenocorticism, the nephrotic stage of glomerulonephritis and in occasional patients with diabetes, terminal lymphomas and congestive heart failure. The gamma globulin values obtained by electrophoresis correlated fairly well with the levels obtained by a chemical method and with those estimated by $ZnSO_4$ turbidity. Hypoalbuminemia was observed to a variable degree in most of the patients with diseases associated with elevation of the gamma globulin, as well as in some of those with normal and depressed globulin levels.

The quantitative data are presented and characteristic patterns demonstrated. Also, electrophoretograms of urine proteins in patients with the nephrotic syndrome and multiple myeloma are shown and compared with the serum protein patterns. The effect on the protein patterns of standing for 24 hours at room and refrigerator temperatures have also been studied. These results and the relationship to alteration in the flocculation tests under these conditions are also presented.

The simplicity of filter paper electrophoresis, the convenience of the small amounts of serum that can be used, and the clinical correlations of the data make this an extremely useful clinical technic.

NEOPLASTIC DISEASE

Functioning Islet Cell Tumor Masquerading as Spindle Cell Neoplasm. *L. J. McCormack,* Penn G. Skillern,* J. S. Hewlett, and George Crile.** Cleveland Clinic, Cleveland.

Two patients with proved organic hypoglycemia due to hyperinsulinism were relieved of their symptoms by the removal of 1 tumor from each. The tumor in the first patient was located in the right thorax, a most unusual location, and probably originated from ectopic pancreatic tissue. The tumor in the second patient probably originated from the pancreas. Both tumors were very large, weighing 2440 Gm. and 4720 Gm., respectively. Each tumor was composed of 2 types of cells. The most predominant type of cell was a spindle shaped cell with long cytoplasmic fibrils. The other type of cell was a round cell without fibrils, resembling the beta cell. Occasionally, in such a round cell in the tumor removed from the second patient, blue granules such as are seen in the normal beta cell were seen. No metastases could be demonstrated arising from either tumor. The first patient is living and symptom-free 1½ years after the operation. The second patient has had no recurrence of hypoglycemic symptoms or tumor 6 months postoperatively. It is important that this rare type of islet cell tumor be recognized, so that it will not be misdiagnosed as fibrosarcoma.

PHARMACOLOGY AND THERAPEUTICS

A New Pharmacologic Property of Quinidine: Protein Anabolic Effect. *Robert H. Furman,* R. Palmer Howard* and Edward C. Reifenstein, Jr.* Oklahoma Medical Research Institute and Hospital, Oklahoma City.

The biologic properties of quinidine and its levo-isomer quinine are said to differ only quantitatively. Stereoisomerism does not alter the plasmocidal activity significantly. However, it may explain why idiosyncrasy to quinine often extends to other

levorotary Cinchona alkaloids, but rarely to the dextrorotary compounds. As another qualitative difference between these 2 substances, therefore, it is of interest to report our observation that quinidine sulfate orally has a protein anabolic effect not shared by quinine sulfate administered orally.

A 67-year-old female with postmenopausal osteoporosis was placed on a metabolic balance regime to evaluate the effects of long-acting testosterone esters. During her study, spontaneous auricular fibrillation developed and was treated successfully with quinidine sulfate. Subsequently, analysis of the balance data indicated that quinidine had induced a definite protein anabolic effect. The response to quinidine sulfate was studied a second time in this patient with the same dosage schedule as before. There was a prompt decrease in urinary nitrogen and phosphorus excretions and a gain in body weight. A repeat study with quinine sulfate in the same dosage revealed no significant anabolic effect.

The discovery of this unexpected quinidine sulfate effect may be important because: (1) it may augment our knowledge of the cardiovascular effects of quinidine, (2) it reveals a protein-anabolic action of an organic substance which differs chemically from compounds with known protein-anabolic activity and which may lead to other new agents with this activity, and (3) it may increase our understanding of the process of protein anabolism.

The Uricosuric Effect of Phenylbutazone. *E. R. Huffman, C. J. Smyth, George M. Wilson, Jr.* and Robert Hill.** V. A. Hospital, Denver.

The uricosuric effect of oral phenylbutazone (600, 800 and 1200 mg./24 hr.) on the serum uric acid and 24-hour urine uric acid excretion has been studied in 10 gouty and 6 nongouty arthritics. Phenylbutazone blood levels are available in 11 of the patients. A step-wise fall of serum uric acid to normal level occurred in all but 2 of the gouty patients: 1 went into congestive failure and the other received a dosage of 600 mg./24 hours. The serum uric acid fell an average of 4.1 mg. % by the 8th day. There were no apparent differences between the groups who received 800 and 1200 mg. of phenyl butazone per 24 hours. A lag of 2 or 3 days occurred before there was any appreciable fall in the serum uric acid. The excretion of uric acid was increased in all instances, except in the patient with congestive heart failure. The increase was in a step-wise fashion and usually reached a maximum between the 2nd and 6th day of therapy. The average increase of uric acid excretion per 24 hours in the gouty arthritics was 243.5 mg. and in the nongouty arthritics 177 mg.

The 6 nongouty arthritics behaved similarly to the gouty patients except that the average fall in uric acid was less—2.9 mg. on 800 and 1200 mg., and 1.7 mg. on 600 mg. dosages of phenylbutazone.

Average phenylbutazone blood levels for dosages of 600, 800 and 1500 mg./24 hours were 14.7 mg. %, 15.4 mg. %, and 20.4 mg. %, respectively.

Clinical Studies of an Antiemetic Agent: Chlorpromazine. *Ralph W. Knight,* Bartis Kent,* George Morris* and Stanley Rogers** (introduced by *J. H. Moyer*). V. A. Hospital, Baylor University College of Medicine, Houston.

Chlorpromazine [10-(γ-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride] (S.K.F. 2601-A), in preliminary laboratory and clinical studies exhibits antiemetic properties, presumably by central nervous system block of vomiting reflexes. This is a preliminary report on 71 patients with established nausea and vomiting who received Chlorpromazine 25 mg. to 50 mg. orally or parenterally. A majority received 1 to 4 doses. Fifty-four had excellent, 14 good, 1 fair, and 2 poor control of their nausea and vomiting. With variations from mild to marked degree, 41 exhibited sedation, 26 dizziness, 15 dry mucous membranes, 16 tachycardia, and 15 hypotension.

Eighteen in this series received Chlorpromazine for 3 to 24 days, with an average course being 7.5 days. Frequency ranged from once daily to once every 3 hours. The over-all control of nausea and emesis was: 12 excellent, 5 good and 1 fair. In varying degrees, 14 exhibited sedation, 6 dizziness, 3 dry mucous membranes, 7 hypotension. Three patients in the total series, receiving only 1 dose of chlorpromazine, exhibited significant side effects.

Eight additional normal adults without nausea and on no medications were given 1 50 mg. dose of Chlorpromazine. Seven exhibited sedation, 3 dizziness, 2 dryness of mouth, and 2 slight hypotension. Six of these given 50 mg. IM and ECG studies immediately prior and 1 hour later exhibited no significant ECG changes.

A More Effective Form of Administering Ammonium Chloride. *A. A. Camara and F. R. Schemm.* Great Falls, Montana.

Ammonium chloride is the most frequently used acid diuretic. It is commonly administered as an enteric coated tablet, compressed into a hard mass, and is relatively insoluble even after its coating has disappeared. Prosectors and roentgenologists frequently find large numbers of such tablets undissolved in the colon. Experimental subject, D. M., who received a total of 390 mEq. of chloride as enteric coated NH_4Cl tablets over a period of 3 days while on a constant diet eliminated 90 mEq. of it in the stools. Thus 23% of the medication was not absorbed. Nonabsorption is, of course, even more pronounced in debilitated patients.

Ammonium chloride powder packed loosely with an equal amount of calcium carbonate in a gelatin capsule has been found to be effectively absorbed both experimentally and in clinical prac-

tice. Experimental subject, A. C., while subsisting on a daily constant diet, ingested a total of 732 mEq. of chloride as ammonium chloride in capsule form over a period of 4 days. Only 2.0 mEq. of chloride daily was found in the stool collected during that period, as against 1.7 mEq. daily during the preceding period when no ammonium chloride was taken, signifying virtually complete absorption of the drug. Further proof of its absorption is the elimination of 765 mEq. of chloride in the urine in excess of the basal urinary chloride excretion. In clinical practice, ammonium chloride given in the capsule form has been found to be effective in much smaller doses than the enteric coated form.

The Comparative Efficacy of Various Mercurial Diuretics. *Ralph V. Ford, Charles L. Spurr and John H. Moyer.* Departments of Medicine and Pharamacology of Baylor University College of Medicine and the V. A. Hospital, Houston.

Twelve male patients with mild to severe congestive heart failure have been studied to: (1) illustrate an approach for the evaluation of diuretic agents using controlled metabolic technics and (2) compare the relative diuretic efficacy of Mercuhydrin, Thiomerin, Neohydrin and SU 1775 (Ciba) when administered parenterally, as well as Neohydrin administered orally.

The patients were studied on the metabolic ward with a constant sodium, water, and caloric intake. An effort was made to wait until the patient was returned to an identical weight before the various diuretic agents were administered. The data suggest that, when this study was ideal in these respects, the changes in water, sodium, chloride, and potassium excretion, as well as weight, were more statistically significant.

The organic mercury thiol diuretic, SU 1775 (Ciba), was the most potent diuretic agent studied and was entirely free from local pain or other untoward effects which could be attributed to the drug per se. Four different dosages of SU 1775 were used (equivalent to 20, 40, 80, and 160 mg. Hg). Three dosages of the other 4 agents were used (20, 40, and 80 mg. Hg equivalents). At the 40 mg. Hg equivalent dosage, the average percentage increase in sodium excretion was 368 for SU 1775, 277 for Neohydrin parenterally, 214 for Mercuhydrin, 191 for Thiomerin, and 109 for Neohydrin orally. The slope of the dosage response curve was greatest for SU 1775.

The use of controlled metabolic conditions to insure constant weight (and salt and water load) is suggested in evaluating diuretic agents.

The "Delayed Therapocorticoid Effect": A Previously Undescribed Action of Adrenal Hormones Important for Successful Treatment of Eye Disease. *William Q. Wolfson and James R. Quinn.** The Rackham Arthritis Research Unit, Department of Internal Medicine, and the Department of Ophthalmology, University of Michigan Medical School, Ann Arbor; and the Unit for Clinical Investigation, Department of Internal Medicine, Wayne University College of Medicine, Detroit.

Individualized long-acting corticotropin treatment has induced sustained remission without subsequent relapse in 89% of 35 patients with acute eye lesions and in 63% of patients with chronic disorders, all previously reported to respond irregularly to hormones. In 15 patients who received an average 14,700 units of corticotropin during 455 days, recovery appeared dependent upon an effect of adrenal hormones fundamentally different from their usually prompt action. After prolonged treatment of acute disorders involving 1 optic nerve or retina, some patients also showed improvement in chronic "irreversible" lesions involving the other eye. Persistent treatment restored normal or useful vision in both eyes without later relapse. Subsequently, similar results were obtained in patients with only chronic "irreversible" neuroretinal disorders. At best, improvement begins slowly and its onset may be delayed for up to 300 treatment days. Maximum improvement usually requires ½ to over 2 years treatment, and maintenance dosage is necessary. Slow progressive improvement often preceded by prolonged therapeutic latency constitutes the "delayed therapocorticoid effect," so far observed only in disorders of neuroectodermal derivatives. Certain observations suggest it involves restitution of structures which do not regenerate in eucorticoid individuals.

RESPIRATORY SYSTEM

Glossopharyngeal Breathing. *Roy H. Behnke** *and Ralph C. Wilmore** (introduced by *Kenneth G. Kohlstaedt*). Indiana University Medical Center, Department of Medicine, Indianapolis.

A few patients with chronic respiratory paralysis due to poliomyelitis develop a peculiar voluntary method of respiration—glossopharyngeal breathing. Using the mouth, cheeks, tongue, pharynx, and larynx they force air into the lungs. The patient gulps air with an open glottis, closing it after each gulp, trapping the air. After lung capacity is reached, usually after 6 or 7 such gulps, the glottis is released and passive expiration follows.

The purpose of this study was to determine the physiologic efficiency of glossopharyngeal breathing. It was performed upon a 25-year-old chronic

poliomyelitis respiratory invalid. On a rocking bed cycling at 20 per minute he had a 535 cc. tidal volume, and an arterial oxygen saturation range of 92.5–95.0%.

The average tidal volume with normal thoracic respiration was 267 cc., giving a 4,000 cc. minute ventilation: rate of 15 per minute. After 5 minutes of "normal" breathing the arterial oxygen saturation fell to 71.4%.

With glossopharyngeal breathing the patient had an average tidal volume of 780 cc.: 248 cc. with thoracic respiration and the remaining 532 cc. effected by 6 or 7 gulps each with an average volume of 86 cc.

Glossopharyngeal breathing, 11 cycles per minute, contributed 5,650 cc. of total 8,580 cc. minute ventilation. The range of arterial oxygen saturation up to 45 minutes was 91.5–92.1%.

Intratracheal pressure was measured through the tracheotomy stoma with a water manometer. With the glottis closed, just prior to the first gulp, the pressure became positive, 3.5–4.0 cm. H_2O. Each succeeding gulp raised the pressure 1.0 to 1.2 cm. End intratracheal positive pressure was 10–12 cm. H_2O.

Glossopharyngeal breathing is a physiologically efficient voluntary type of respiration in this patient.

The Response of Abnormal Pulmonary Function to Intermittent Positive Pressure Breathing (IPPB). *Richard N. Westcott.* Cleveland Clinic, Cleveland.

Since an inconstant clinical response to IPPB aerosol therapy has been reported and observed in various chronic pulmonary disorders, an attempt was made to elucidate the changes in pulmonary function attributable to this therapy, using the Bennett Pressure Breathing Therapy unit (Model TV-2P). In 21 subjects, of whom 13 presented obstructive emphysema, 5 bronchiectasis, and 3 pulmonary fibrosis as the major problems respectively, pulmonary function tests were performed both before and after (24 hours or more) a 2 to 3 week course of IPPB for 20 minutes twice daily. Nine of the 21 subjects had definite evidence of cor pulmonale and secondary polycythemia. The data obtained included spirograms with measurement of the vital capacity and its subdivisions, determination of residual volume by the helium dilution method, maximum breathing capacity, and response of ventilation and arterial oxygen saturation to a standard exercise test.

Clinical response was simultaneously judged according to changes in exercise tolerance, exertional dyspnea, prominence of wheezing and coughing, and character and quantity of sputum.

In 14 of the subjects, a significant improvement (av. 32.2%) in maximum breathing capacity was attributed to the IPPB aerosol therapy, and in each of these patients there was a definite clinical improvement. The remaining 7 patients failed to improve clinically or in their maximum breathing capacity. No other correlation could uniformly be made between clinical change and alterations in the measured components of pulmonary function. Several interesting patterns of response were observed, however, in the data obtained following IPPB therapy. These appeared to be conditioned by (a) the individual control pattern of pulmonary function, and (b) the participation of bronchial spasm and infection in the initial pulmonary insufficiency. These observed patterns of response and their apparent relation to control observations are presented.

Changes in Composition of Pneumoperitoneum Air in Human Subjects Following Injection of Ambient Air. *H. G. Boren,* D. E. Jenkins and Clark Silverthorne** (introduced by *C. L. Spurr*). V. A. Hospital and the Department of Medicine of Baylor University College of Medicine, Houston.

This is a study of the chemical composition of pneumoperitoneum air and of the rate of change following injection of ambient air. Thirty-two male patients, 25 to 67 years of age, 29 with pulmonary tuberculosis and 3 with emphysema, were studied. Gas analyses were done on 11 patients by the Van Slyke method and on 21 patients by the Haldane technic. The more accurate Haldane data are presented. No significant difference was noted between the Van Slyke and Haldane values. Average refills were 1050 cc. at 1 week and 1200 cc. at 2 weeks. Specimens 1 and 2 weeks following refill showed a mean composition as follows CO_2, 6.08%, ±0.093; O, 4.90%, ±0.42; N, 88.95%, ±4.72. The preinjection composition of gas was similar in the groups receiving refills at 1 and 2 weeks. In 6 patients, repeated analyses over a 2-month period showed marked stability of composition. These values were altered by the addition of ambient air, but reverted at differing rates to their initial values. Initial pneumoperitoneum with 1000 cc. of ambient air showed a significant increase in CO_2 within 1 minute (0.31%), reaching 1.88% in 10 minutes, 2.96% in 20 minutes, and 5.82% in 24 hours. Little change in the oxygen composition was noted during the first 20 minutes (19.85%), but significant change was found at 24 hours (6.17%), and at 1 week (3.83%). It is felt that the rate of change of carbon dioxide concentration is sufficient in magnitude and rapidity to be important in practical therapeusis.

Abstracts Submitted to the Annual Meeting of the Eastern Section of the American Federation for Clinical Research

Children's Medical Center, Boston, Massachusetts • Monday, January 4, 1954

BLOOD

Absence of Serum Gamma Globulin in an Adult. *Jay P. Sanford,* Cutting B. Favour,* and Melvin S. Tribeman.* Harvard Medical School, Peter Bent Brigham Hospital, Boston.

A case with absence of serum gamma globulin in the presence of relatively normal quantities of the other protein factors in an adult is described, which presented itself as bronchiectasis and a "sprue-like syndrome" associated with repeated infections including Hemophilus influenzae meningitis as an adult and a paraplegia presumably due to poliomyelitis.

The syndrome of agammaglobulinemia in an adult simulates the condition previously described in children closely enough so that the diagnosis can be entertained on clinical grounds. Screening of suspected cases can be done with isohemagglutinin titers, since these cases have no isohemagglutinins. The diagnosis is made by quantitative chemical or immunochemical determination of the gamma globulin fraction.

Survival studies of injected gamma globulin revealed a half-life of about 20 days in children, hence, the defect in metabolism seems to be a lack of production rather than excessive destruction.

Probably most children with this disease have not survived to reach adult life, and its recognition has been delayed. Since the defect is probably amenable to correction by replacement therapy, and it may be possible to prevent permanent crippling resulting from various infections, the diagnosis is of considerable importance.

Thymoma and Refractory Anemia. *Stuart C. Finch, Joseph F. Ross, Russell B. Street,* and John W. Strieder.** Evans Memorial, Massachusetts Memorial Hospitals and Boston University School of Medicine, Boston.

An unusual syndrome consisting of a benign thymoma and refractory anemia has been observed in 2 adult female patients. The relationship between the simultaneous occurrence of these 2 uncommon entities in the same individuals has been studied, and compared with 7 similar cases reported by others. Both experimental and clinical observations suggest that certain relationships between thymic and hematopoietic tissues may be of importance in the pathogenesis of this syndrome.

Hematologic studies on these individuals revealed complete aplasia of bone marrow erythroid elements, decreased reticulocytosis, and a normocytic normochromic anemia. No alterations of granulocytic and thrombocytic elements of either the peripheral blood or bone marrow have been noted. Differential erythrocyte agglutination studies and radioiron utilization determinations indicate normal erythrocyte survival and virtual absence of erythrocyte production. The thymic tumors removed from these patients were composed primarily of swirls of spindle cells often in the form of pseudorosettes intermingled with focal areas of thymic cell hyperplasia.

Therapy in these patients has consisted primarily of multiple transfusions, and transfusion hemosiderosis has been observed in 1 subject. Erythrocyte regeneration has not occurred in response to thymectomy, splenectomy, and to the administration of ACTH, cortisone, and other pharmacologic agents.

Observations on the Nature of the "Anemic" Factor. *Allan J. Erslev and Paul H. Lavietes.** Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The production of red blood cells has recently been shown to be influenced and possibly regulated by a humoral factor found in plasma from anemic animals. The biochemical and biologic nature of this "anemic" factor was studied in rabbits.

Plasma, serum and serum protein fractions were obtained from rabbits in which previous bleedings had depressed the hemoglobin to less than 7 Gm. %. Fifty ml. of these fluids were administered I.V. once a day for 4 days to normal rabbits and daily hemo-

globins and reticulocyte counts were made. The results indicate that the "anemic" factor is attached to or behaves like a serum albumin, alpha globulin or beta globulin.

A study was made of the possibility that the "anemic" factor is identical with the bone marrow stimulating factor which Jacobson has shown might be produced in intact reticuloendothelial or lymphatic tissue.

The function of these tissues was impaired in rabbits by administering nitrogen mustard. One hour later the rabbits were made anemic by repeated bleedings and "anemic" serum was obtained 2 days later. Fifty ml. of this serum was administered once a day for 4 days to each of 8 normal rabbits. A group of 7 rabbits received "anemic" serum from donors having been bled in the same way but without first receiving nitrogen mustard. No significant difference was found in the reticulocyte response of the two groups. This seems to indicate that the "anemic" factor is not related to Jacobson's factor and is not produced by the reticuloendothelial, the lymphatic or the hematopoietic tissue.

The Incorporation of Radioactive Iron in Human Foodstuffs. *James A. E. Halkett,* and Joseph F. Ross.* Radioisotope Unit, Boston V.A. Hospital, Boston.

With the advent of radioisotopes, extensive investigations have been carried out on the absorption of inorganic radioactive iron from the enteric tract. Of more fundamental importance is the study of the absorption of "food" iron from the digestive tract. To investigate this problem, we have employed biologic and physiologic technics to incorporate radioactive iron in food as "metabolically bound" iron. Such radioactive iron-labelled foodstuffs can then be used in human subjects to investigate the absorption of food iron.

One of the most common foods is the green vegetable leaf. In order that the absorption of iron from plant tissues could be studied, we have labelled different plant leaves with radioiron by growing plants in a nutrient solution containing radioactive iron. Using this technic, we have studied the mechanism and the rate of incorporation of radioactive iron in the roots and in the leaves, and have investigated various factors which influence iron metabolism by plants. We have found that the assimilation of iron occurs at a much faster rate than has previously been reported.

One of the principal sources of iron in the American diet is thought to be the chicken egg. To label eggs with radioiron, chickens were injected with radioactive iron through the wing vein and this iron was incorporated in the eggs very rapidly and in high percentage. The radioactivity of the eggs laid immediately after the injection of radioactive iron was very high, but it progressively decreased in the eggs laid during the next 22–24 days. At the 22nd to 24th day, however, there was an abrupt increase in the radioactive iron contained in the freshly laid eggs, even though there had been no reinjection of radioiron. This periodic variation in the radioiron content of the eggs was traced through 4 cycles in each of several hens and is believed to be related to the life span of the chicken erythrocyte.

Radioactive iron also is being incorporated into meat foodstuffs and into yeast and chlorella. The latter substances may possibly provide an inexpensive and readily procurable source of food iron.

The Absorption of "Egg" and Inorganic Iron by Normal, Iron-Deficient, and Hemochromatotic Subjects. *R. B. Chodos, J. F. Ross, M. Pratt,* J. Donovan, and J. Halkett.** V.A. Hospital, Boston.

Iron absorption has been evaluated in subjects with normal, diminished, and increased iron stores. Radioactive iron as labeled chicken eggs or as ferrous chloride was administered orally. The quantity of iron incorporated into hemoglobin and the unabsorbed iron recovered in the feces were determined by gamma counting technics. Seventy-five such studies have been completed, including multiple studies of both egg and inorganic iron absorption by individuals with normal and abnormal iron stores. Whatever the status of the body iron stores, egg iron was uniformly less well-absorbed and utilized than was ferrous chloride. However, the actual quantity of iron absorbed did seem to be directly dependent upon the body iron stores. Thus, iron deficient subjects absorbed far more iron than normals, while patients with increased iron stores of established hemochromatosis absorbed less iron than normals. After marked depletion of these excess iron stores of patients with hemochromatosis by repeated venesection, both egg and inorganic iron absorption was markedly increased over that observed in hemochromatosis prior to venesection or in normals. It is probable that this increased absorption in these patients is dependent upon the production of either an absolute or relative iron deficiency, and suggests that iron stores in hemochromatosis will be reaccumulated after the venesection program unless efforts are made to limit iron absorption or venesections are periodically repeated.

The Relationship between Gastric Acidity and the Absorption of Iron from the Upper Gastrointestinal Tract. *William J. Grace, Ronald K. Doig,* and Harold G. Wolff.* Departments of Medicine and Psychiatry, New York Hospital-Cornell Medical Center, New York.

The absorption of iron was studied by the iron tolerance curve in a fistulous subject in whom simultaneous measurements of gastric acidity could be made at half hourly intervals following the administration of a test dose of ferrous or ferric iron. The results of 27 experiments show that, although there

was considerable variation in the absorption of iron from day to day in this subject, the absorption bore no direct relationship to the level of gastric acidity. The absorption was either great or small at high levels of acidity (pH 1–2) or at low levels of acidity (pH 5–7).

Ten iron absorption studies were performed on 9 patients who exhibited histamine refractory achlorhydria. The results indicate that the absorption of iron is as great as in those with adequate free hydrochloric acid. Seven "normal" persons were studied and later restudied after taking large doses of sodium bicarbonate with the test dose of iron. The absorption of iron in each of these individuals was the same, whether or not sodium bicarbonate was taken.

The results of these studies indicate that iron absorption from the upper gastrointestinal tract is not dependent upon the presence of hydrochloric acid or the degree of gastric acidity, but is probably related to some as yet undefined function of the upper small intestine.

The Use of Radioactive Iron in the Evaluation of Erythropoiesis and Ferrokinetics. *Myron Pollycove,* Robert B. Chodos, Leonard Apt,* and Joseph F. Ross*, with the technical assistance of *Mary Pratt, Joan Donovan, and John Sullivan.* Radioisotope Unit, Boston V.A. Hospital, Boston.

Tracer doses of plasma protein-bound Fe^{59} were administered by intravenous injection to normal individuals and to patients with various types of erythropoietic dysfunction.

Prior to the Fe^{59} injection, plasma and red cell volumes were determined by simultaneous use of Evans Blue dye and P^{32}-labelled red blood cells. Employing gamma ray counting technics, the clearance time (in hr.) of Fe^{59} from the plasma, the turnover rate (in mg./24 hr.) of plasma iron and the utilization of iron (in %) in the formation of circulating hemoglobin were determined. The anatomic distribution of Fe^{59} was measured simultaneously by external body survey with a mobile scintillation detector. Employing these methods, the movement of iron was measured in the circulating plasma, the circulating red blood cells, and in various body tissues of special significance in erythropoiesis and iron metabolism.

Patterns of iron metabolism and kinetics determined in various types of anemia were found to differ markedly and significantly from the normal. It is possible to demonstrate that erythropoiesis is progressing only in the spleen and liver and not in the marrow in certain patients with myelofibrosis, and that in certain pathologic states tissue iron metabolism utilizes a much larger fraction of the daily plasma iron turnover than is utilized in the formation of circulating hemoglobin. These functional studies are correlated with chemical and morphologic changes in the peripheral blood, bone marrow, and spleen. These studies of the kinetics of iron metabolism employing Fe^{59} have considerable value in the diagnosis and clarification of the pathogenesis of disorders of the hematopoietic system and are a helpful adjunct in selecting proper therapy.

The Absorption of Vitamin B_{12} after Total Gastrectomy. *Allyn B. Ley, and L. E. Sharpe.** Memorial Center for Cancer and Allied Diseases, New York.

Although there is a preponderance of evidence that the stomach is the sole site of production of intrinsic factor, the development of pernicious anemia in patients who have been subjected to total gastrectomy has been an irregular occurrence. It seemed pertinent, therefore, to study the absorption of vitamin B_{12} in such patients. Because routine hematologic and microbiologic methods are not applicable to such a study, use was made of vitamin B_{12} tagged with Co^{60}. This material, in 0.5 μg. to 1.0 μg. doses, was administered to totally gastrectomized patients. Stools were subsequently examined for radioactivity, using a scintillation counter, according to a modification of a method originally described by Heinle, et al. Subjects studied thus far have included 2 normals, 1 patient with pernicious anemia, and 6 patients with total gastrectomy.

The normal patients absorbed approximately 65% of the administered dose. The patient with pernicious anemia, in early remission, absorbed approximately 22% of the dose; when the same dose was administered with a source of intrinsic factor, the absorption increased to 49%. The gastrectomized patients showed results quite similar to the patient with pernicious anemia: the absorption of the vitamin alone varied from 0 to 22%; when the same dose was given with a source of intrinsic factor the absorption increased and varied from 36 to 59%.

One patient, who had been gastrectomized 5 years before this study, was found to have a mild but definite macrocytic anemia with a hematocrit of 35%. The bone marrow aspirate on this patient showed equivocal megaloblastosis. The patient was then treated with vitamin B_{12}, 5 μg. by mouth each day. During the ensuing 7 weeks there was a fall in the hematocrit to 32.8%. He was then treated for the subsequent 8 weeks with the same daily dose of vitamin B_{12} administered with an intrinsic factor concentrate (Lederle), following which there was a rise in the hematocrit to 43% with a decrease in mean corpuscular volume nearly to normal.

These results are interpreted to demonstrate the importance of the gastric mucosa in the absorption of vitamin B_{12}.

Scintillation Measurements of the Uptake of Radioactive Vitamin B_{12} in Humans. *George B. Jerzy Glass, Gerald A. Gellin,* and Loukia Stephenson.*

Department of Medicine and Gastroenterological Research Laboratory, New York Medical College, Flower and Fifth Avenue Hospitals, New York (aided by a Research grant from the National Institute of Arthritis and Metabolic Diseases, National Institute of Health, Public Health Service).

The metabolic turn over of vitamin B_{12} in humans has been evaluated heretofore by means of blood, urine and feces studies. To obtain new information a method of measuring the uptake and distribution of radioactive vitamin B_{12} in the human body was developed. Over 2200 scintillation surface counts were taken over various skin projections of underlying organs in 16 normal and pathologic individuals following parenteral and oral administration of Co^{60}-labelled vitamin B_{12}, whereby doses of Co^{60} were used far below the permissible maximum in man.

In normals, as well as in patients with pernicious anemia, and after total gastrectomy within 2 hours after I.M. injection of 5–10 μg. of radioactive vitamin B_{12} (0.185–0.925 μc. Co^{60}) about 95% of injected material disappeared from the site of injection and radioactivity rose to peak values over kidneys, spleen, iliac crest and, later, over extremities. It required, however 5 days to build up the peak of radioactivity over the liver. The counts over the liver exceeded those over other areas of the body several times, and they declined extremely slowly, so that 86–94% of peak radioactivity was found over the liver after 3 months.

Following ingestion of radioactive vitamin B_{12}, highest counts are found initially over the upper left abdomen, from where they shift to mid- and lower abdomen during the next 24 hours. With normal bowel function the counts over the entire abdomen fall to a minimum within 5 days, with the exception of the liver which shows a steady increase in counts up to the 5–7th day. At that time the liver counts exceed many times those over the rest of the abdomen, the difference being statistically highly significant, and they remain at this level almost stationary for the next few months.

The long storage of vitamin B_{12} in the liver may easily explain the prolonged time needed for depletion of stores of vitamin B_{12} and development of macrocytic anemia after total gastrectomy, as well as long remissions observed in pernicious anemia following treatment with liver extracts or vitamin B_{12}.

Uptake of Radioactive Vitamin B_{12} by the Liver: Test for Intestinal Absorption of Vitamin B_{12} and Measure of the Intrinsic Factor Activity. *George B. Jerzy Glass.* Department of Medicine and Gastroenterological Research Laboratory, New York Medical College, New York (aided by a research grant from the National Institute of Arthritis and Metabolic Diseases, National Institute of Health, Public Health Service).

Using the method of scintillation counting of the hepatic uptake of ingested Co^{60}-labelled vitamin B_{12} in 8 controls and 8 patients with macrocytic anemias, a test procedure was developed for quantitation of intestinal utilization of vitamin B_{12} in humans and measurement of intrinsic factor activity. By comparing the increments in liver counts following ingestion and injection of a standard dose of radioactive vitamin B_{12} in the same individual one can calculate the parenteral equivalent, as well as percentual utilization in intestines of ingested amounts of vitamin B_{12}. If the hepatic uptake is defective the oral test is repeated after normal human gastric juice or intrinsic factor concentrate from hog stomach is added to the same oral dose of vitamin B_{12}. This determines whether or not the absorption defect depends upon the absence of the intrinsic factor. The test of hepatic uptake of ingested Co^{60}-vitamin B_{12} in pernicious anemia can be also used for evaluation of the potency of unknown materials tested for intrinsic factor activity.

In nutritional and hemolytic anemias with normal gastric secretion, hepatic uptake of ingested radioactive vitamin B_{12} was normal, but in 3 patients with pernicious anemia in relapse and remission it was negligible or nil. This gave direct indication of defective transport of ingested vitamin B_{12} to the liver in pernicious anemia. The liver uptake became normal after the same dose of Co^{60}-vitamin B_{12} was ingested together with 75–95 cc. normal human gastric juice. Thus, the ability of normal gastric juice to promote the transfer to ingested vitamin B_{12} through intestinal wall to the liver was directly demonstrated, the reason for intestinal block to utilization of vitamin B_{12} being the absence of intrinsic factor from the gastric juice.

In sprue, hepatic uptake of vitamin B_{12} was also negligible, but it was not corrected by addition of normal human gastric juice or intrinsic factor concentrate from hog stomach. This indicated that the defective intestinal absorption of vitamin B_{12} in sprue was not dependent on the absence of intrinsic factor but the absorption defect in the intestinal wall itself.

Nasal Instillation and Inhalation of Crystalline B_{12} in the Treatment of Pernicious Anemia. *Raymond W. Monto and John W. Rebuck.** Division of Hematology and Department of Laboratories. The Henry Ford Hospital, Detroit.

Twelve cases of pernicious anemia in relapse were treated with vitamin B_{12} by nasal instillation or inhalation. Three of these patients received crystalline B_{12} in physiologic saline by vaponephrin nebulizer. B_{12} lactose powder was administered to 1 patient by a dust inhalator. Nasal instillation of vitamin B_{12} in saline was utilized in the last 8 cases.

Twenty patients with pernicious anemia in

remission were given inhalation and nasal instillation therapy. They were treated at comparable intervals to parenteral maintenance therapy.

Inhalation, nasal instillation, and direct administration of B_{12} into the pulmonary tract resulted in urinary excretion of detectable amounts of the vitamin. Mucous membrane irritation or sensitization has not been encountered to date.

Complete clinical and hematologic remission was obtained in all 12 patients treated by this technic. Twenty patients with pernicious anemia in remission have been maintained by inhalation and nasal instillation of B_{12} for 18 months. This simple method of therapy is an effective, economical, and safe mode of treatment for pernicious anemia.

Platelet Prothromboplastin (PP): Description of a Method of Assay, Isolation, and some of its Properties. *Herbert S. Sise,* Dionysios Adamis,* and Delbert Kimball** (introduced by *Joseph Stanton*). Tufts Medical School, Boston City Hospital, Boston.

Although the existence of platelet thromboplastin has been known for years, definitive means of assay and isolation have been lacking. In the present study, it was found that by passage of oxalated beef plasma through Seitz filter pads (Republic GP grade) and collection of the filtrate in aliquots, certain of these aliquots contained sufficient prothrombin and accessory factors for a Quick prothrombin time of 20–24 seconds, but that simple recalcification, without addition of thromboplastin, resulted in no clot formation. Restoration of recalcification time to 6–14 minutes can be achieved by adding a 1:10 dilution of normal plasma, or a suspension of washed pletelets collected from native human plasma, which platelets have then contacted glass; but platelet poor native human plasma or purified PTC did not restore recalcification times to normal. Further studies showed this factor to be stable at temperatures up to 38°C but that it was destroyed by heat at 56°C for 9 minutes. PP is adsorbed by barium sulfate and can be eluted with sodium citrate. Platelet poor oxalated plasma which is collected in glass containers possesses a normal amount of PP. PP appears in the supernatant of a centrifuged sample of suspended washed platelets after contact with glass. Before contact with glass, the factor remains with the platelet fraction. PP is measured as the soluble substance after it is released from platelets. The concentration can be reduced to about 20% in a system before very significant prolongation of clotting time becomes apparent, and a further decrease to 5% rapidly prolongs clotting time to infinity. PP is present in serum but to a less extent than plasma, thereby implying its consumption during the process of clotting. PP is considered to be the precursor of plasma thromboplastin and the conversion of PP to thromboplastin is accomplished with the aid of AHG and presumably PTC and PTA. Differentiation from other coagulation factors is made and its presence in "purified" preparations of other clotting factors is discussed.

A Disorder of Blood Coagulation in Systemic Lupus Erythematosus. *Stanley L. Lee and Martin Sanders.* The Mount Sinai Hospital, New York (aided by a grant from the National Institute of Arthritis and Metabolic Diseases, National Institute of Health, Public Health Service.

Thirty-one consecutive cases of systemic lupus erythematosus were studied from the point of view of blood coagulation. Coagulation times of whole blood and recalcified plasma, prothrombin time, prothrombin consumption, thrombin generation, thromboplastin generation, mixtures with normal bloods and plasmas, antithrombin and antithromboplastin tests were performed by standard methods. Ten of the 31 showed evidence of a disorder of coagulation, varying in degree but of the same type in all patients. In its full-blown form, this consisted of prolonged clotting time, prolonged plasma clotting time, slight elevation of prothrombin time, normal or slightly impaired prothrombin consumption but definitely delayed thrombin generation, and evidence of increased resistance to the action of thromboplastin. Whole blood or plasma from these patients, when added to normal blood or plasma, delayed coagulation significantly. Six patients showed this complete syndrome. The other 4 had insufficient prolongation of clotting time to demonstrate an anticoagulant effect on normal blood, but showed definite increase in antithromboplastin.

In these patients all the abnormal clotting phenomena can be explained as being due to the presence of a circulating anticoagulant which has been shown to inhibit the action, but not the formation of thromboplastin. This anticoagulant is stable for long periods in stored plasma, resists heating to 56°C. for 30 minutes, and has been separated with the gamma globulin fraction.

There are 31 cases of naturally occurring circulating anticoagulants in the world literature. Of these, only 2 are cases of L.E. (Conley 1952). It now seems that circulating anticoagulants occur with considerable frequency in L.E.

The L.E. cell factor has been shown to depend on the presence of thromboplastin for its action on leucocytes. The possible relationship between the L.E. cell factor (present in all 31 cases) and the demonstrated circulating anticoagulant is discussed.

Control of Bleeding Manifestations in "Fibrinolytic States" by Corticotropin and Cortisone. *Lucy Salomon* and Mario Stefanini* (aided by a Grant from the American Heart Association). New England Center Hospital, Boston.

Eight patients with bleeding manifestations of excessive fibrinolysis received high doses of corticotropin or cortisone. They included 3 cases of dis-

seminated prostatic carcinoma, 2 cases following thoracic surgery, 2 cases following prostatectomy for benign adenoma, 1 case of fibrinogenopenia in premature separation of placenta. Effect of hormones administration was noted at frequent intervals on: (a) bleeding manifestations, (b) lytic activity in whole blood and plasma, (c) fibrinolysin, profibrinolysin and antifibrinolysin activity in plasma and serum determined by original technics, (d) activity and concentration of coagulation factors (particularly fibrinogen).

In disseminated prostatic carcinoma (where the output of fibrinolytic enzyme(s) is continuous) corticotropin or cortisone control of bleeding occurred after several hours, parallel to rise in plasma fibrinogen level and drop in plasma fibrinolytic activity. In the remaining cases (where activation of fibrinolysin was acute but transitory) control of bleeding was prompt (life-saving in 2 cases which were not in irreversible shock). Administration of plasma may have aided in controlling the hemorrhage in the latter group of cases. In all instances, decrease of plasma fibrinolytic activity appeared due to decrease in available plasma profibrinolysin, and, principally, to rise in plasma antifibrinolysis. In comparable doses corticotropin was more effective than cortisone.

Intramuscular Trypsin in Thromboembolic Disease. *Irving Innerfield.* Jewish Memorial Hospital, New York.

Parenzyme in oil, an intramuscular trypsin preparation, was administered to 25 guinea pigs in varying dosage. A dose range of 10–20 mg. per injection regularly produced local tissue necrosis. A dose range of 2.5 to 5.0 mg. per injection did not produce local tissue damage grossly, but a mild inflammatory reaction was noted in 4 instances. Parenzyme in doses of 2.5 mg. or less, however, did not produce gross or histologic evidence of tissue injury.

Parenzyme was then administered in 2.5 mg. doses, t.i.d. for 3 to 7 days in the lower thigh of patients scheduled for mid-thigh amputation. Grossly, there was no evidence of irritation in overlying injection sites. Following amputation, microscopic examination of injected muscle areas was not remarkable.

Parenzyme has been given to 1742 patients who have now received an average of 8 intramuscular injections. Each dose contains 2.5 mg. of trypsin. A 1% systemic reaction has been noted. The only local side effect observed is a mild to severe erythema at the injection site in approximately 3 to 5% of the patients. Pain at the injection site is usually mild and of brief duration. Local necrosis or sterile abscess formation at the injection sites has not been observed. Clinically, highly favorable results were obtained in 64 of 72 patients with acute thrombophlebitis, 19 of 26 patients with phlebothrombosis of 2 to 14 years duration, 39 of 51 patients with diabetic cellulitis and superficial ulcerations of the foot, and 16 of 21 patients with recent pulmonary emboli.

Physiologically, in the dose range employed, trypsin is not anticoagulant, but a thrombolytic and anti-inflammatory agent. The clotting time and clotting proteins remain unchanged. Thrombi show early canalization and eventual lysis. The mechanism of these effects appears to be related to trypsin-induced activation of plasminogen into plasmin.

It is concluded that intramuscular trypsin therapy with Parenzyme in oil is clinically safe, and effective in disease states characterized by thrombi and/or an acute inflammatory reaction.

The Effect of Heparin on Phenol Turbidity and Serum Lipids in the Postabsorptive State. *Bernard A. Sachs, Paxton Cady* and Leo Rain.** Medical Division, Montefiore Hospital, New York (aided by a grant from the Lasdon Foundation).

Heparin sodium was administered intravenously to 17 normal subjects and 8 patients with disorders not associated with atherosclerosis, and its effect on the phenol turbidity test, serum cholesterol, lipid phosphorus and total lipids was studied at intervals for a period of 3 hours.

The 25 subjects received 10,000 I.U. (100 mg.) heparin. Thirteen of these exhibited a marked rise in turbidity units, reaching a peak in ½–1 hour followed by a fall to or below fasting levels. Nine others exhibited a similar rise but did not return to fasting levels at the end of 3 hours. Two subjects exhibited a fall, and 1, no significant change. Heparin was added to the fasting serum from 10 subjects and incubated at 38°C. for similar intervals. In vitro, no change in turbidity units was noted for any of the subjects. When 1% protamine sulfate was added in vitro to the serum from patients who received heparin in vivo, the effect on phenol turbidity was completely negated.

In contrast to the elevations observed in phenol turbidity, all of the 15 subjects in whom total lipids were determined showed a drop following heparin (mean fall = 15%) which was primarily due to a fall in neutral fat. Lipid phosphorus fell in 14 of 17 subjects (mean fall = 14%) and the total cholesterol remained the same. Determination of lipoproteins by paper electrophoresis revealed a migration of the predominant lipid band from the region of beta-globulin toward alpha-2-globulin following heparin.

The marked changes in phenol turbidity may be explained by the reduction in size of serum lipoproteins following heparin.

The Effect of Blood Lipids on the Anticoagulant Activity of Heparin. *Jerome M. Waldron, K. Knox,* and Garfield G. Duncan.** Department of Physiology, Temple University School of Medicine and

Division of Medicine, Pennsylvania Hospital, Philadelphia.

It has been assumed that the lipemia-clearing and anticoagulant activities of heparin are independent but parallel functions of the molecule. Previous work in dogs has shown that the lipemia-clearing activity of heparin was associated with a decrease in its anticoagulant activity. Because of the widespread interest in the use of heparin in human atherosclerosis the relation between lipids and anticoagulant activity of heparin was investigated.

The in vitro and in vivo heparin sensitivity of the blood was determined before and after the oral ingestion of fat in the form of cream or corn oil. A complete silicone technic and a collodion technic were employed in measuring clotting time. One-half hour after feeding the fat the in vitro sensitivity to heparin (technic of Jaques) was decreased from that of a fasting control sample. There was still a significant decrease in sensitivity 2 hours after the fat had been ingested, but normal sensitivity had returned in 3 hours. The in vivo sensitivity was determined by injecting 500 I. U. (5 mg.) of heparin I. V. two hours after feeding the fat. The changes in clotting time after the fat were also determined. Two types of response in heparin sensitivity were obtained, and these correlated with the effect of fat on clotting time. If the oral ingestion of fat resulted in an accelerated clotting time the sensitivity to heparin was decreased. If the oral ingestion of fat did not alter the clotting time, the sensitivity to heparin was increased. The mutual interaction of heparin and blood lipids must be considered in the use of heparin in the treatment of atherosclerosis. In efforts to separate the lipemia-clearing factor and the anticoagulant factor of heparin, this mutual interaction must be evaluated.

CARDIOVASCULAR SYSTEM

The Hemodynamic Effects of Acute Anemia with Special Reference to Coronary Resistance and Flow in the Presence of Coronary Insufficiency. *Robert B. Case,* Erik Berglund,* and Stanley J. Sarnoff.* Department of Physiology, Harvard School of Public Health, Boston.

Cardiac output, left main coronary artery flow, right and left atrial pressures and pulmonary artery and aortic pressures were continuously recorded in the open-chest dog. From these data derived values were calculated for right and left ventricular stroke work, and coronary, peripheral and pulmonary vascular resistances.

The hematocrit was varied from 49.5% to 17.5% by replacement of blood with dextran, and a full ventricular work performance (Starling curve) analysis was made at each of the 5 hematocrit levels.

It was found that normal coronary vessels could dilate to a remarkable extent, the coronary PRU going from 0.8 at the highest hematocrit to 0.23 at the lowest hematocrit level. As evidenced by ventricular performance analysis, this coronary dilation could compensate for the decreased O_2 transport capacity of the blood down to a hematocrit of 32%. At 24% the Starling curve was definitely lowered. At 17% a frank failure curve with a descending limb was obtained.

In the dog in which coronary insufficiency was simulated by compromise of the coronary lumen, further compensatory vasodilation could not occur and left ventricular failure occurred at lesser degrees of anemia.

These data provide: (1) quantitative evidence regarding the added hazard of anemia in the presence of coronary insufficiency, (2) basic information regarding the determinants of coronary flow, (3) the effect of acute anemia on ventricular function, and (4) the effect of acute anemia on cardiac output and peripheral and pulmonary vascular resistances.

Atrial Septal Defect: Relationship of Interatrial Pressure Gradient to Right and Left Ventricular Work and the Effect of Operative Closure. *Roger B. Hickler* and Walter T. Goodale.* Harvard Medical School, Peter Bent Brigham Hospital, Boston.

Cardiac catheterization was performed on 4 cases of uncomplicated atrial septal defect before and after surgical closure of the defect. Cardiac outputs were measured by the direct Fick method and pressures were measured by a Sanborn electromanometer. In 3 of these the left atrial mean pressure was obtained by direct passage of the catheter through the defect. In the 4th preoperative case, and in the postoperative recatheterizations where the catheter could not be passed into the left atrium, the left atrial pressure was deduced from the pulmonary capillary-venous "wedge pressure."

Analysis of the effects of surgical closure revealed: (1) a significant postoperative fall in right atrial and rise in left atrial mean pressures, (2) a significant fall in all cases in right ventricular stroke work, attending a marked diminution or abolition of the left-to-right shunt, and (3) a significant rise in left ventricular stroke volume and stroke work.

In 12 cases of uncomplicated atrial septal defect, a catheter was passed directly through the defect, and then withdrawn, to obtain a reliable interatrial mean pressure gradient. With a high sensitivity electromanometer, these mean pressure gradients appeared accurate to within ±0.5 mm. Stroke

volume and stroke work for each ventricle were also measured and plotted against the interatrial gradient.

Analysis of the curves obtained revealed the following: (1) A fall in interatrial gradient from a normal level of approximately 5 mm. to nearly zero occurred with progressively large left-to-right shunts through the defect. (2) A fall in left ventricular stroke volume was apparent when the interatrial gradient fell below 2 mm. Hg, associated with a marked rise in right ventricular stroke volume. (3) With diminishing interatrial gradients there was a progressive fall in left ventricular work and accelerative rise in right ventricular work. At negligible interatrial gradients with maximal left-to-right shunts, the right and left ventricular works were essentially equalized.

Conclusions: (1) In atrial septal defect there is decreased left atrial and increased right atrial mean pressure with an immeasurable interatrial gradient in the very large shunt group. (2) Identical or parallel changes in the end diastolic filling pressures of the right and left ventricle may be assumed. (3) The increased filling pressure of the right ventricle accompanied increased right ventricular stroke volume and work, while decreased filling pressure of the left ventricle resulted in decreased left ventricular stroke volume and work. (4) Each ventricle thus responded to changes in its own filling pressure by corresponding changes in stroke work.

These observations appear to be an expression of the application of Starling's Law of the Heart in man.

A Quantitative Analysis of Circulatory Dynamics in Aortic Stenosis. *Richard Gorlin, Michael B. Mathews, Raymond Daley,* Ian K. R. McMillan,* and W. E. Medd, Jr.** Harvard Medical School, Peter Bent Brigham Hospital, Boston.

Seventeen patients with predominant aortic stenosis were studied at rest by cardiac catheterization. Of these, there were 10 exercise and 6 atropine studies. Fick, cardiac outputs and pressures were measured. In addition, left ventricular (LV) pressures were obtained at operation in 1 with AS and 1 with AS MS. Postmortem cyclic perfusion of these 2 aortic valves and another with AS AI under simulated in vivo conditions made possible direct measurement of LV pressures and hydraulic calculation of same from photographic measurement of stenotic and regurgitant valve areas. Thus, total cardiac output, LV systolic pressure and work were determined in 3 patients. The latter 2 were increased 2- and 3-fold respectively in pure AS (0.4 $cm.^2$ area). LV output and systolic pressure were doubled and work quadrupled in AI AS, while all 3 were decreased in AS MS.

In the other 14 patients, only effective work could be estimated. Relationship of pulmonary capillary diastolic (PCd) pressure (LV filling pressure) to effective work was normal in 12, and this was unchanged by atropine cardiac acceleration. Exercise, however, resulted in increased PCd in all, regardless of clinical status, but had little effect on cardiac work. Clinical disability increased as cardiac output diminished. PCd bore no relation to clinical severity.

Effect of critical stenosis (0.5 $cm.^2$), magnitude of work load, and effects of AI and MS were defined. Stenotic valve pressure-flow relation was found to be fixed, despite variations in output. When AI was present, tachycardia reduced regurgitation volume. Tachycardia itself seemed well-tolerated.

Visualization of Valvular and Cardiac Calcification by Planigraphy. *Jacob Zatuchni, Herbert Fisher* and Louis A. Soloff.* Departments of Medicine, Episcopal and Temple University Hospitals, and Department of Radiology, Episcopal Hospital, Philadelphia.

A preoperative diagnosis of valvular calcification which indicates advanced degeneration and implies potential immobility is now more than of academic interest. It is also of importance in uncovering aortic valvular disease that may contraindicate mitral commissurotomy. Conventional roentgenography, including overexposure and a short focal point, uncovered valvular calcification in only approximately ¼ of those who had calcification demonstrated at operation. Fluoroscopy, in our hands, has a much greater positive yield, but has the disadvantages of failing to supply a permanent verifiable record.

A planigraphic technic of visualizing valvular calcification is described. Of 12 consecutive positive studies by this method, 8 had calcification limited to the mitral valve, 1 to the aortic valve and 3 demonstrated calcification in both the aortic and mitral valves. Two individuals showed calcification of the left auricular wall.

Of these 12, conventional roentgenography demonstrated calcification in only 2, both limited to the mitral valve.

Vectorcardiographic Patterns in Combined Ventricular Hypertrophy. *Gerald H. Whipple and Harold D. Levine.* Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston.

Spatial vectorcardiograms have been recorded in normals and in a heterogeneous group of cardiac patients by means of bipolar leads arranged according to the "perfect cube" method. Several patterns suggestive of combined ventricular hypertrophy have been observed during preliminary analysis of this material, particularly in patients with rheumatic valvular deformities. These patterns may be classified as variants of the usual simple right or left ventricular hypertrophy patterns recorded by this method, with 1 exception. In this latter type, the most characteristic features are

found in the horizontal plane vectorcardiogram, in which the QRS loop has a roughly elliptical shape with the major axis of the ellipse lying in the anteroposterior direction and with approximately equal development of the loop anteriorly and posteriorly. The significance of these findings has been assessed in the light of the clinical, electrocardiographic and roentgenologic data, and where available, the results of cardiac catheterization, autopsy, and the impressions obtained during cardiac surgery.

A Correlation of the Ballistocardiogram and Angiocardiograms with Simultaneous Reproduction. *Herbert R. Brown, Jr. and Theodore B. Steinhauser.** The Highland Hospital Cardiac Laboratory, Rochester, New York.

The use of the ballistocardiogram in its empiric analysis of the subject is reviewed in its present state of development. Particular emphasis is related to the field of degenerative processes which involves the heart.

The apparatus used in this clinic is so devised as to correlate simultaneously the ballistocardiogram with specific angiocardiographic photographs. This is accomplished by placing the x-ray tube underneath the ballistograph table and thus obtaining the x-ray films and the ballistocardiographic record simultaneously.

The further interpretation and evaluation of angiocardiograms is enhanced by a simple procedure of making 10 to 20 frame exposures of each radiograph made during the angiocardiographic study. This method is particularly useful when radiographs are made at a rate of 1 or 2 per second.

The resulting movie film animates the "still" angiocardiogram, adding materially to interpretation of the radiographic findings. The application of this procedure is demonstrated by 2 case examples.

The Effect of Neosynephrin Administration on Stroke Volume, and Ballistocardiographic Amplitude Determined by the Dock Electromagnetic Instrument. *N. Robert Frank and Henry J. Kowalski.* Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

The relationship of changes in ballistocardiographic wave amplitude to alterations in stroke during Neosynephrin administration was investigated in 24 hospitalized patients without cardiovascular disease. Minute volume of flow was measured directly by the dye-injection method of Hamilton in 10 subjects. The Dock electromagnetic ballistocardiograph equipped with a 50 m.f.d. condenser was employed to approximate displacement in 14 other patients before, during, and after drug administration.

Under the influence of intravenously administered Neosynephrin, the stroke volume increased consistently ($p < .01$), while systolic and diastolic pressures rose and bradycardia developed. The minute volume was unaffected. The ballistocardiographic tracings showed significant decreases ($p < .01$) in the amplitude of the I, J, and K waves without changes in their duration. In some instances there was complete, but reversible, distortion of the control wave pattern.

Thus, the changes in stroke volume and ballistocardiograms developed in opposite directions. It is concluded that the ballistocardiographic technic, using the described instrument, is unsatisfactory for defining the cardiovascular forces in terms of blood flow.

Cardiac Pain in Man: Blocking Effect of Ethyl Chloride Spray on the Angina of Ergonovine. *Seymour H. Rinzler, Isidore Stein,* Hyman Bakst,* Joseph Weinstein,* Robert Gittler* and Janet Travell.** Cardiovascular Research Unit, Beth Israel Hospital, New York, V. A., Regional Office, Brooklyn, and Department of Pharmacology, Cornell University Medical College, New York. This investigation was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service, and in part by the Josiah Macy, Jr. Foundation and the Loyal League Philanthropies.

In this investigation we studied the blocking effect of ethyl chloride spray on the pain and electrocardiographic changes induced by intravenous ergonovine maleate in the patient with effort angina but a normal resting electrocardiogram.

Thirty-six tests were done on 7 such patients (44 to 70 years, 5 males and 2 females) who, following intravenous injection of ergonovine maleate (0.1–0.4 mg.), promptly developed an abnormal electrocardiogram and also pain in the chest, shoulder, arm or neck similar to that induced by effort. In all 7 patients, intravenous injection of physiologic saline in the same volume produced neither pain nor electrocardiographic changes. Nitroglycerin (0.4 or 0.6 mg.) given sublingually prior to ergonovine prevented both pain and electrocardiographic changes in 5 of the 7 patients. When ethyl chloride was applied to the potential pain areas just *before* ergonovine was injected, in 4 of the 7 patients it prevented the predicted painful response to ergonovine but not the changes in the electrocardiogram. When ethyl chloride spray was applied *after* ergonovine had been injected and pain had appeared, spraying with ethyl chloride relieved pain completely in 4 of 6 patients and partially in the other 2, despite persistence of the electrocardiographic changes, until nitroglycerin was given.

This study confirms the previously reported efficacy of ethyl chloride spray for relief of the somatic component of cardiac pain. Furthermore,

modification of the usual ergonovine test by prior application of ethyl chloride spray provides a pharmacologically controlled stress test for coronary insufficiency which has the advantage of eliminating the associated pain in a large proportion of patients.

Transcapillary Migration of Deuterium Oxide and Thiocyanate in the Lungs of Man. *Lawrence S. Lilienfeld,* Edward D. Freis, Edward A. Partenope and Harold Morowitz.** Cardiovascular Research Laboratory, Georgetown University Medical Center and V. A. Hospital, Washington, D. C.

In this study the transcapillary migration of thiocyanate and deuterium oxide is determined for the pulmonary capillaries of normal human subjects utilizing the method previously employed in this laboratory for studying the movement of these substances from the forearm capillaries. Through a cardiac catheter a mixture of D_2O, SCN and T-1824 dye is injected rapidly directly into the pulmonary artery segment and samples of blood are withdrawn from the femoral artery during the period of 1 circulation. From determinations of the arterial concentration of the T-1824 dye the concentration of SCN and D_2O expected—if there was no transcapillary loss of these substances—is calculated. From the measured amount of SCN and D_2O actually found in the samples the % plasma loss is easily determined.

The results show that in the pulmonary circulation only, 0–10% of the thiocyanate ion is lost compared with 70% previously found for the forearm circulation, and that these losses are almost constant throughout the period of the first circulation. Deuterium oxide behaves quite differently in that in the forearm about 95% is constantly lost throughout the circulation period, whereas in the lung the losses amount to approximately 40% early, but before the first circulation period is completed the losses become gains of approximately 40%, indicating appreciable reabsorption. The significance of these results, which may be due largely to anatomic differences between the lungs and the forearm, is discussed.

Intermittency of Flow in Larger Vessels of the Human Forearm. *Edward A. Partenope, Edward D. Freis and Lawrence S. Lilienfeld.** Cardiovascular Research Laboratory, Georgetown University Medical Center and V. A. Hospital, Washington, D. C.

If T-1824 dye is injected in sufficient concentration (5 cc. of 0.5% solution) into the brachial artery, the dye appears in the skin, thus permitting cinematography of its passage through the dermal circulation. Instead of the expected uniform coloration from the point of injection distally, it was observed that the dye was distributed in segments of approximately 2 to 10 cm. in diameter. Distal segments often exhibited dye before some proximal segments. There often was considerable delay from the appearance in one segment as compared to adjacent segments. Similarly, dye disappeared more rapidly from one area than from another. This suggests that there is intermittency of flow of the arteries supplying these segments similar to the intermittency previously described for capillaries.

Intradermal histamine produced rapid and intense coloration of dye in that segment, as compared to other areas in the forearm, showing that vascular resistance in the segment had been markedly reduced.

Similarly, the intra-arterial injection of Priscoline abolished the segmental distribution of dye in the forearm and replaced it with a rapidly appearing and disappearing diffuse coloration. Conversely, intradermal injection of epinephrine prevented the appearance of dye in the injected segment.

These observations provide evidence for the first time that there is a fluctuating state of tone in arterial vessels which can be influenced by local vasodilating and vasoconstricting agents. Color motion pictures are used to illustrate these phenomena.

Renal Responses to Acute Alterations in Intracranial Pressure in Patients with and without Congestive Heart Failure. *William Hollander* and Walter E. Judson.* Boston University School of Medicine, Robert Dawson Evans Memorial Hospital, Boston.

Changes in intracranial pressure were produced either by removing cerebrospinal fluid or infusing saline through a lumbar puncture of the subarachnoid space. The pressure was reduced as low as 50 mm. of water and raised as high as 600 mm. of water for 5 to 20 minutes.

The results indicate that: (1) In normal and compensated hypertensive individuals acute alterations in cerebrospinal fluid pressure produced little or no change in renal plasma flow, glomerular filtration rate, or excretion of salt and water. (2) In some patients with congestive heart failure or superior vena caval block, in which the cerebrospinal fluid pressure is already elevated, a reduction of the cerebrospinal fluid pressure may cause significant increases in sodium excretion in the range of 25 to 100% without changes in GFR.

It is concluded that changes in intracranial pressure may play an important role in the retention of sodium in diseases associated with chronic venous congestion of the head.

The Effect of Intravenous Reserpin Upon the Blood Pressure of Hypertensive Subjects. *Alfred M. Sellers* and Joseph H. Hafkenschiel.* Hypertension Section, Edward B. Robinette Foundation, Medi-

cal Clinic, Hospital of the University of Pennsylvania, School of Medicine, University of Pennsylvania, Philadelphia (aided by a grant from the Southeastern Pennsylvania Heart Association).

A study of Reserpin (Ciba Serpasil), a crystalline alkaloid of *Rauwolfia serpentina*, was prompted by the report of testing in animals by Plummer et al. (Federation Proc. *12:* 357, 1953). Reserpin was administered by intravenous infusion to 17 hypertensive patients. Electrocardiograms and ballistocardiograms were done before and during the infusion. The total dose of Reserpin varied from 1.6 to 5.5 mg. or 0.022 to 0.073 mg./Kg. The infusion time ranged from 41 to 80 minutes. The drug was given in an infusion of 300 cc. of physiologic salt solution. The infusion rate ranged from 0.54 to 1.26 μ/Kg./min.

Fifteen patients showed a hypotensive effect, 9 during the infusion and 6 following an average latent period of 4 hours. The maximum effect passed in 24 hours, but frequently the pressures were lower than before Reserpin. Only 2 patients had no fall in pressure. The effective dosage was 0.060 to 0.073 mg./Kg. and effective infusion rate 1.0 μ/Kg./min. The average fall in mean pressure for 17 patients was 42 mm. The drug was equally effective in patients having azotemia, even when they also had diastolic pressures over 140. In 2 normotensive controls the fall in mean pressure averaged only 9 mm.

Side reactions were: sedation, relaxation, nasal congestion. Postural hypotension was prominent. Nausea, vomiting and dyspnea were less common. There was no change in heart rate during the infusion. No significant changes were noted in the electrocardiogram or ballistocardiogram.

Although this constitutes a preliminary report on relatively few patients, it raises the question of the use of Reserpin in hospitalized patients to determine the responsiveness of those who might be candidates for the oral drug.

The Effect of Large Doses of Cortisone on First Attacks of Rheumatic Carditis. *I. G. Kroop, E. T. Heffer,* R. D. Turin* and S. R. Slater.** Divisions of Medicine (Cardiovascular Research) and Pediatrics, The Jewish Sanitarium and Hospital for Chronic Disease, Brooklyn.

The beneficial effects of cortisone on polyarthritis and on the nonspecific or constitutional manifestations of rheumatic fever is universally acknowledged. Also, the suppressive effect of cortisone usually controls the immediate clinical manifestations of acute carditis, including congestive heart failure. However, there is some question as to whether cortisone prevents or significantly reduces residual damage to the myocardium and valves. Our data show that early, intensive and individualized dosage of cortisone may prevent residual cardiac damage in patients followed for 3 to 30 months after cessation of treatment.

Nineteen children between 5 and 15 years of age suffering from their first attack of rheumatic fever with acute carditis were treated with 200–300 mg. of oral cortisone divided into 4 doses every 6 hours. This initial dose was continued at times for 2 weeks or longer, until there was suppression of clinical and laboratory signs of activity. Then reduction in dosage was considered. If there were signs of activity on lower dosage, higher dosage was resumed immediately. Therefore, duration of treatment varied between 20 and 54 days and the total dose between 2.0 and 9.7 Gm. Supportive therapy included a 200–500 mg. sodium diet supplemented with vitamins, and 200,000 units of oral penicillin prophylaxis daily.

There was no residual cardiac involvement in 12 patients treated early, 9 within the first 2 weeks, and 3 within the first 3 weeks of illness. There was residual cardiac damage in the remaining 7 patients, 6 of whom were treated after more than 3 weeks of illness. All patients developed moon-face and weight gain, but no serious side effects with the high and prolonged dosage employed.

COLLAGEN DISEASES—ALLERGY

The C-Reactive Protein Determination as a Measure of Rheumatic Activity. *I. G. Kroop, E. T. Heffer,* and N. H. Shackman.** Division of Medicine (Cardiovascular Research) and Pediatrics, The Jewish Sanitarium and Hospital for Chronic Disease, Brooklyn.

In recent years, several groups of investigators have reported the value of the C-reactive protein determination in acute rheumatic fever. It is generally agreed that the test is nonspecific and not of diagnostic value. However, it seems to be a sensitive index of the presence of rheumatic activity.

This report concerns itself with the observations made on 24 patients with rheumatic fever; 2 patients had chorea and carditis. Twenty patients were treated with cortisone, hydrocortisone, or ACTH. Complete study and follow-up of the cases were accomplished by the same group of physicians. The absence of rheumatic activity was judged by the complete absence of all clinical and laboratory manifestations of the disease. Because of the limited amount of C-reactive protein antiserum available to us, the test was performed at strategic points in

the clinical course when there was a question of rheumatic activity.

Our results indicated that there was a very close correlation between the inactive state and a negative C-reactive protein determination. However, there were 2 cases of a negative C-reactive protein in the presence of rheumatic activity. A positive test in 2 cases of chorea was associated with carditis. Cortisone therapy eliminated the C-reactive protein from the patient's serum. A positive test after discontinuation of cortisone represented either a "rebound phenomenon," or continued activity. In general, the C-reactive protein determination was a better guide to activity than the sedimentation rate, and was used as a criterion for ambulating the patient when the sedimentation rate was elevated.

A Clinical Evaluation of Electrophoresis in Rheumatic Fever. *I. G. Kroop, E. T. Heffer* and N. H. Shackman.** Divisions of Medicine (Cardiovascular Research) and Pediatrics, The Jewish Sanitarium and Hospital for Chronic Disease, Brooklyn.

Previous electrophoretic studies have failed to establish a characteristic diagnostic pattern, and have not differentiated the immune response of the rheumatic from the nonrheumatic patient, particularly following streptococcal disease. With these limitations in mind, electrophoresis was employed together with the sedimentation rate, blood fibrinogen, protein flocculation tests, and the C-reactive protein determination, in order to help determine the presence or absence of rheumatic activity. An analysis of 40 electrophoretic determinations of the serum proteins in 36 patients is the basis of this report.

It should be stressed that a beta globulin elevation was encountered in 7 of our 30 patients with rheumatic fever, whereas this fraction is rarely elevated in the postinfectious period of normals (1 out of 36 patients). Although not specific, an elevated beta globulin fraction should therefore strongly suggest the diagnosis of rheumatic fever.

Our data confirm the variability and nonspecificity of the other electrophoretic abnormalities in rheumatic fever. Changes in the alpha-1, alpha-2, and gamma globulins, alone, and in combination, were observed.

A normal electrophoretic pattern may be obtained in the presence of rheumatic activity. Electrophoretic abnormalities may persist when the disease is inactive clinically, and when the C-reactive protein determination is negative. Therefore, electrophoresis is of no absolute value in determining rheumatic activity.

The Cause of Hypercalcuria in Sarcoidosis. *Philip H. Henneman, Anne P. Forbes, Eleanor F. Dempsey,* Evelyn L. Carroll,* and Fuller Albright.** Medical Service of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston.

A male patient with sarcoidosis was investigated with a complete balance study for calcium, phosphorus, nitrogen, sodium, potassium, and chloride. The study was divided into 6 days pre-therapy control, 30 days cortisone therapy, and 12 days post-therapy control.

Initially the patient exhibited hypercalcemia and hyperphosphatemia, a slightly negative nitrogen balance, and markedly negative calcium and phosphorus balances. On a diet containing 292 mg. of calcium, the fecal calcium was only 23 mg., while the urinary calcium averaged 930 mg. Cortisone produced a fall in serum calcium, a step-like fall in urinary calcium to a minimum of 216 mg. daily and an irregular rise in fecal calcium to a maximum of 417 mg. daily. On discontinuing cortisone the urinary calcium rose to 448 mg. per day.

The mechanism leading to hypercalcemia and hypercalcuria in this patient appears to be excessive absorption of calcium from the gastrointestinal tract in a pattern suggesting hypervitaminosis D. That excessive absorption is not the entire explanation is indicated by a urinary calcium excretion markedly in excess of dietary intake, a relation which could be explained, however, by the second or parathyroid-hormone-like action of vitamin D.

This study confirms an earlier study of the calcium balance in sarcoidosis, and may explain the absence of major bone decalcification despite prolonged hypercalcuria in certain patients with sarcoid.

ENDOCRINES AND METABOLISM

The Effect of Metabolic Activity upon the Concentration of Inorganic Iodide by Surviving Thyroid Slices. *Norbert Freinkel and Sidney H. Ingbar.* Thorndike Memorial Laboratory II and IV Medical Services (Harvard), Boston City Hospital, Department of Medicine, Harvard Medical School, Boston.

Ionic iodide is the substrate for the initial oxidative phenomena of organic iodinations. Thus, in the thyroid, the selective ability to concentrate inorganic iodide may act as a rate-limiting factor in the synthesis of thyroid hormone, since the availability of substrate will be determined by the magnitude of concentration differentials for iodide between thyroid and blood. Little is known about the mechanisms whereby such thyroid/blood gradi-

ents are established. In the present studies, the problem has been investigated in vitro to permit broader approaches than are possible in the intact animal.

Concentrations of inorganic I^{131} by sheep thyroid slices were examined in the Warburg apparatus and related to simultaneous estimation of cellular oxygen consumption. Organic binding was eliminated by the addition of 1-methyl-2-mercapto-imidazole to the suspending medium. It has been found that the accumulation and retention of inorganic I^{131} in vitro can be modified by simple manipulation of pH, oxygen tension, and temperature. This functional dependence of iodide transport upon the availability of energy derived from cellular metabolism implicates an active energy-linked process in the establishment and maintenance of concentration differentials between thyroid and perfusate.

The Relationship of Iodine Stores in the Thyroid to Iodide Ion Accumulation. *W. P. Vander Laan.* New England Center Hospital, Boston.

In hypophysectomized rats receiving thyrotropin in constant doses, the capacity of the thyroid gland to accumulate iodide ion was found to be enhanced by measures which had in common a tendency to lower the hormonal stores of the thyroid gland, as indicated by the total iodine content. These included iodine restriction and treatment with propylthiouracil and with potassium thiocyanate. In the instance of thiocyanate, the drug was withdrawn 24 hours before thyroid:serum iodide ratios were measured to allow recovery of the concentrating mechanism from inhibition. A similar reciprocal relationship between iodide-concentrating capacity and total thyroid iodine was found in intact animals.

Since it is known that a rising iodide ion concentration in the thyroid gland, below inhibitory levels, increases the rate of binding of iodine to protein, a self-regulatory mechanism of the thyroid gland is postulated, and this mechanism appears at least partially independent of the pituitary.

The significance of this in regard to the relative constancy of thyroid-bound iodine and in regard to Graves' disease is discussed.

The Turnover Rate of l-Thyroxine and l-Triiodothyronine in Euthyroid Subjects as Measured by Radioiodine-Labeled Compounds. *Kenneth Sterling, Joyce Lashof* and Evelyn B. Man.** Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Radioactively-labeled l-thyroxine or l-triiodothyronine in tracer amounts was injected intravenously in euthyroid patients hospitalized for rehabilitation. Serum butanol extractable iodines were normal.

Patients received an excess of nonradioactive iodine during studies to minimize thyroid uptake and reutilization of radioiodine liberated on degradation of the administered compounds.

Serum radioactivity was measured on blood samples drawn 10 minutes after injection, and daily for 2 weeks. There was a rapid initial fall, attributed to a distribution phase. Within 2 days after injection of radiothyroxine, the serum radioactivity declined more gradually, assuming a straight line on semilogarithmic plot. This slow exponential component of the disappearance curve was interpreted as indicating thyroxine turnover, or the rates of formation and degradation, which in a steady state are identical. The mean half-time of thyroxine turnover in 6 subjects was 6.7 days.

The disappearance curve observed after injection of labeled triiodothyronine was much more rapid, with a mean half-time of 2.7 days in 4 subjects. Successive studies with l-thyroxine and l-triiodothyronine in 1 individual clearly demonstrated the more rapid disappearance of the latter compound.

Adrenal Cortical Function and the Blood Pyruvate and Lactate Response in Man. *Thomas F. Frawley and Raul D. Alfaro.** Department of Endocrinology and Metabolism, Albany Medical College and Metabolic Clinic, Albany Hospital, Albany, New York.

Three phases of the relationship in man of adrenal cortical function to blood lactic and pyruvic acid following intravenous glucose (0.5 Gm per Kg. body weight as a 20% solution) have been investigated. The first deals with deficient adrenal cortical function due to Addison's disease or panhypopituitarism; the second, with excessive adrenal cortical activity—the result of Cushing's Syndrome or ACTH and cortisone therapy; and, the third with the effect of a constant infusion of Compound F.

Contrary to observations in animals, patients with adrenal cortical insufficiency have not shown low blood values of lactic and pyruvic acids. Decreased lactate-pyruvic acid ratios were observed and the calculated pyruvic acid-excess was increased in untreated adrenal cortical insufficiency. This suggests an increased production or decreased rate of utilization of pyruvic acid in such states. With intravenous glucose there was a rise in pyruvic acid and lactic acid similar to that observed in normal individuals.

Two distinct patterns in pyruvic acid metabolism develop in patients during ACTH or cortisone therapy. On a moderate dosage of these agents the fasting levels of pyruvic and lactate remain normal, but after glucose administration pyruvic acid shows increased and prolonged elevation. With excess dosage an abnormal rise in fasting pyruvic acid develops and there is also a prolonged elevation of pyruvic acid with administered glucose. Both dosage schedules may produce there changes without a significant change in glucose tolerance. During

a constant infusion of Compound F in normal medical students at rates of 12 mg. and 25 mg. per hour there was no significant effect on glucose tolerance or pyruvate-lactate metabolism. It is concluded that with normal pancreatic reserve short-term high levels of Compound F do not interfere with glucose, pyruvate, lactate production or metabolism.

The adrenal cortex influences pyruvate and lactate metabolism under certain circumstances independently of any measurable changes in glucose metabolism. The observation of elevated pyruvic acid in opposite states of adrenal cortical function emphasizes the complex nature of the adrenal cortical steroids in intermediary metabolism.

Total Liver Phosphorus: Its Relation to Hepatic Glycogen Storage. *N. Nichols, F. Shertenlieb,* E. Miller* and A. Marble.** George Baker Clinic, New England Deaconess Hospital, Boston.

Cortisone, administered to normal and alloxan-diabetic rabbits for 18 days, caused a 100% increase in liver weight. Diabetes did not alter this response.

The increase in liver size was entirely due to intracellular deposition of glycogen and water. The percentage of intracellular water in the whole liver was unchanged, and its potassium concentration remained constant.

In contrast to the increase in concentration of acid-soluble phosphate associated with hepatic glycogenesis, the concentration of total phosphate fell from 225 (mM/Kg. intracellular water) in glycogen-free livers to 126 in livers where glycogen constituted 50% of the dry solids. A constant P:N ratio of 3.73 (mM P/Gm. N) was found in all livers. In the intracellular water of glycogen-free liver, total phosphate is so high that more than half must be bound, presumably to protein, in an osmotically and electrically inactive state, if the postulates of osmotic equality and electroneutrality are to be satisfied. It is postulated that this protein-bound phosphate, present only in liver, forms an intrahepatic reservoir which, as glycogen is deposited, readily changes its state, entering the pool of acid-soluble phosphate and supplying anion equivalence and osmolar force to the potassium and water that are deposited with glycogen.

The Effect of Drugs upon Copper Metabolism in Hepatolenticular Degeneration and in Normal Subjects. *Walter T. Zimdahl, Irving Hyman* and Edward D. Cook.** Chronic Disease Research Institute, University of Buffalo School of Medicine. Buffalo.

In our initial study the results of a complete copper balance in patients with Wilson's disease and in normal subjects was reported. The present study was undertaken to determine the effects of various drugs upon the copper metabolism in both normal subjects and in patients with Wilson's disease. Each patient was given a thorough history and physical examination and then placed on a complete balance study. Copper intake was measured by taking an aliquot of the food and liquid consumed for each 3-day period. Urine copper and fecal copper were analyzed on 3-day specimens. Copper was estimated in the urine, feces, and food by the method of A. Eden and H. H. Greene. Determination of the copper in the serum was based on the diethyldithiocarbamate reaction described by Gubler. Control blanks were put up each time. After a 6-day control period, the patients were given the drug for the prescribed treatment period.

With the administration of BAL, both the patients with Wilson's disease and the normal controls increased their urinary excretion markedly and showed a negative balance of copper. The patients were given ion exchange resins, and this showed a definite increase in the stool copper. On a normal diet, a negative balance of copper was obtained in patients with Wilson's disease. ACTH induced a marked negative balance of copper, but the patients' symptoms became marked. The patients were also given Versene (disodium calcium ethylene diamine tetra-acetate). This was administered both in an oral and parenteral dosage. The oral dosage caused a very minimal increase in copper excretion. The parenteral dose caused an appreciable effect upon the total excretion of copper. It was felt that although all of these drugs caused an increase in the excretion of copper, the most simple treatment with resin has resulted in satisfactory clinical improvement in all 3 of our patients with Wilson's disease. The effect of ACTH has not been repeated, and the exact significance of this observation is not entirely clear at this point. Because of our previous finding that there is a marked increase of copper absorption through the gut in Wilson's disease, it is recommended that these patients be placed on a low copper diet plus resin therapy.

The Interrelationship of Acute Alkalosis and Potassium Metabolism: A Clinical Study. *Charles R. Kleeman, Milton E. Rubini, Ezra Lamdin,* and Robert F. Kiley, Jr.** Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The role of renal and extrarenal mechanisms in the alkalosis associated with acute potassium depletion has not been clearly defined. An opportunity to investigate this problem was afforded by the parenteral administration of 1600 mEq. (25 mEq./Kg.) of hypertonic $NaHCO_3$ within a 3-hour period to a patient with severe metabolic acidosis due to methanol poisoning. The ensuing alkalosis led to rapid potassium depletion. The patient was studied during 4 metabolic balance periods.

Period 1. Induction of Alkalosis (0–8 hours). The marked acidosis was rapidly converted to a

state of severe metabolic alkalosis. Blood pH rose from 7.02 to 7.55. Approximately ⅓ of the 1350 mEq. of retained sodium remained extracellular as calculated from chloride "space." Urinary pattern was marked by a high rate of ammonia and potassium excretion in an alkaline urine. Potassium clearance/true endogenous creatinine clearance was 1.6.

Period 2. Depletion (8–30 hours). A cumulative potassium deficit of 300 mEq., with hypokalemia occurred. Despite an increasing extracellular alkalosis (pH 7.68), the urine became acid.

Period 3. Repletion (30–56 hours). As cellular potassium losses were replaced, blood pH fell and a reciprocal shift of sodium into the "extracellular space" occurred. Simultaneously, urine ammonia and titratable acid rose abruptly to 4 mEq. and 2 mEq./hr., respectively.

Period 4. Equilibrium (56–104 hours). Full correction of alkalosis with electrolyte and water equilibrium was attained.

Sodium loading, rapid alkalinization and dehydration produced the acute potassium depletion, which, in turn, perpetuated and accentuated the existing alkalosis. It appears that with the extracellular alkalosis of potassium depletion there was a shift of hydrogen ions into cells leading to acidification of the urine. Failure of kidney function to be directed towards correction of the metabolic alkalosis suggests that potassium content and "normal" pH in the renal cell is essential for its response.

The Effect of Oral Protein Feeding Upon Splanchnic Circulation and Metabolism. *J. Leonard Brandt, Leonard Castleman,* John J. Kelly* and Jack Greenwald.** Department of Medicine, State University of New York, College of Medicine at New York City and Kings County Hospital, Brooklyn. (Aided by a grant from Abbott Laboratories.)

The effect of oral high protein feedings upon splanchnic blood flow and oxygen consumption has been examined in 11 subjects (5 normal and 6 with hepatic cirrhosis). These studies have been carried out utilizing the hepatic venous catheterization—BSP technics, and A-V oxygen differences. All subjects were studied in the fasting state and for 2 hours following the ingestion of 250 Gm. of homogenized lean beef. During the control period splanchnic blood flow averaged 1090 cc./min./M.^{2} in the normal group and 865 cc./min./M.^{2} in the cirrhotic group; splanchnic consumption of oxygen averaged 45.4 cc./min./M.^{2} in the normal group and 44 cc./min./M.^{2} in the cirrhotic group. The similarity in oxygen consumption for both groups is accounted for by a greater average A-V oxygen difference in the cirrhotic. The response of the splanchnic circulation to oral feeding showed a striking difference between the 2 groups. Whereas as much as 55% increases in both blood flow and oxygen consumption were demonstrable postprandially in the normal, the cirrhotic seldom showed increases in either flow or oxygen consumption over 25%, and in 2 of the cirrhotics actual decreases in splanchnic oxygen consumption were demonstrable.

In general, postprandial results were the reverse of reported studies with intravenous amino acids which accomplished marked rises in splanchnic oxygen consumption by virtue of increased A-V oxygen differences and no increases in blood flow. The present study revealed postprandial rises in blood flow, no significant change in A-V oxygen differences, with resultant rise in splanchnic oxygen consumption. The interpretation and significance of the data are discussed.

GASTROINTESTINAL SYSTEM

Roentgen Studies of Esophageal Transport in Patients with Dysphagia due to Abnormal Motor Function. *Stanley H. Lorber and Harry Shay.* The Samuel S. Fels Research Institute, Temple University School of Medicine, Philadelphia.

Roentgen studies of esophageal transport were obtained in 31 patients whose chief complaint was dysphagia and in whom no organic obstruction of the esophagus existed. With the patient sitting, 15 cc. of a barium-water mixture were administered orally and esophageal emptying was carefully timed. If emptying was incomplete in 3 minutes, esophageal retention was estimated. Similar observations were made after the consecutive subcutaneous administration of 5 mg. of Urecholine and 30 mg. of Dibuline, each study being performed at the height of drug activity. From the results of parasympathetic stimulation or depression one can divide these patients into 2 groups:

1. In 12 patients the administration of Urecholine produced severe spasm of the lower esophagus similar to that induced by Mecholyl (Kramer and Ingelfinger, Gastroenterology *19:* 243, 1952). Vomiting and substernal discomfort occurred in most. The administration of the parasympathetic depressant Dibuline not only relieved the Urecholine-induced spasm, but was followed, in most, by an increase in esophageal transport over that of the control period.

2. In the remaining 18 patients, esophageal transport remained the same (4) or improved (14) after Urecholine administration, but decreased after the administration of Dibuline.

The physiologic, diagnostic and therapeutic implications of these observations are stressed.

The Correlation of Human Gastric Potentials with Gastric Secretion as Measured by the Electrogastrogram. *Irwin Katzka,* Frederick Jackson Jr.* and Henry M. Lemon.* Evans Memorial Hospital, Boston. (These studies have been aided by research grants from the Massachusetts Division, American Cancer Society.)

The electrogastrogram has been studied by others to diagnose gastric disease, but the physiologic significance of the intragastric potential so measured is not established. Investigations confined to experimental animals have suggested that these potentials are produced by: (1) the degree of acidity of gastric juice, and (2) the electrical energy involved in the production of hydrochloric acid. We have carried out studies in man and have shown that these potentials are related to the process of secretion rather than change in concentration or acidity of gastric juice.

Using intragastric saline electrodes, calomel half-cells and a commercially available potentiometer, we recorded the potentials in the fasting stomach and following the administration of beef broth, histamine or insulin in 45 normal subjects. With histamine or broth, the potential increased rapidly from the fasting level and reached its peak before the maximum increase in gastric acidity occurred. With insulin, the rise in potential began 25–30 minutes later, correlating with hypoglycemia and again preceded maximum acidity. Gastric potentials were not increased by the introduction of acids, alkalies or gastric juice into the stomach. Furthermore, histamine produced no potential change in the stomachs of patients with pernicious anemia or in the esophagus of normals.

The findings to date suggest that electric potential is influenced by gastric secretory activity rather than by the character of the gastric contents. Further studies are planned to determine the effect on intragastric potentials of: (1) gastric motility, (2) carbonic anhydrase inhibitor and (3) ACTH.

The Effect of Anticholinergic Drugs upon Gastric Pepsin Production and Uropepsinogen Excretion. *Harold Silver, Helio Pucci* and Thomas P. Almy.* Department of Medicine, The New York Hospital, Cornell University Medical Center, New York.

The effect of an anticholinergic drug (Banthine 0.2 mg./Kg. I.V.) on basal gastric pepsin secretion was studied in 10 subjects by conventional intubation technic, using a modification of West's coagulation method for pepsin analysis. Pepsin output decreased in every case, with values for the 1st hour after administration averaging 21% of basal (range 8 to 42%). In every case marked dryness of the mouth occurred, often accompanied by tachycardia and blurring of vision.

Further studies were conducted, using the rate of excretion of urinary pepsinogen as an index of the effectiveness of an anticholinergic drug. In 8 subjects, night urines were analyzed during a control period of 7 or more days, during a similar period of oral administration of Probanthine (30 mg. t.i.d., 45 mg. h.s.), and during a subsequent control period. In each subject the mean hourly uropepsinogen excretion rate while receiving Probanthine was less than either of his baseline periods, averaging 78% of control (range 63 to 88%). This decrease is statistically highly significant by t test ($p < 0.01$). All subjects experienced dryness of the mouth, and several had difficulty in voiding, and blurring of vision.

These results show the depressant activity of anticholinergic agents on pepsin secretion under varied circumstances, and it is suggested that this action may be clinically useful in the treatment of peptic ulcer. Studies of uropepsinogen excretion rate have the advantages of reflecting influences on gastric function during the subject's usual activities and over a prolonged period of time, rather than in the brief periods and artificial conditions imposed by direct studies of gastric aspirates.

An Application of Autocorrelation Methods to the Interpretation of Intestinal Motility Records. *John T. Farrar, Melvin D. Small* and John Breen.** Evans Memorial Hospital, Boston and Servomechanisms Laboratory of the Electrical Engineering Department, Massachusetts Institute of Technology, Cambridge.

The interpretation of intestinal motility records has been difficult because the existing methods of analysis do not permit a quantitative evaluation of the complex wave-form which graphically represents the total intestinal motor activity.

The general similarity between intestinal motility records and records of communication signals, such as sound waves, suggested that a method of statistical analysis recently developed in the field of communications might be applied to intestinal motility records. In the application of this method, a complex wave pattern is reduced mathematically to its component parts. Thus, the periodic and random functions which make up the total motor activity may be separated, quantitated and analyzed. The technics used to accomplish this depend on the generation of the autocorrelation function and subsequent Fourier transformation.

We have applied this method to the analysis of human and rabbit intestinal motility records and obtained a quantitative expression for total motor activity, for random activity, and for frequency, amplitude and range of variations of the periodic activity.

INFECTIOUS DISEASES—ANTIBIOTICS

Effects of High Doses of Isoniazid in Man. *Robert D. Sullivan,* Ralph K. Barclay* and David A. Karnofsky* (introduced by *Joseph H. Burchenal*). Chemotherapy Service, Memorial Center for Cancer and Allied Diseases, the Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, and the Sloan-Kettering Division of Cornell University Medical College, New York.

The acute and chronic toxicity of Isoniazid have been described in a number of animal species and striking differences have been observed. The chronic orally tolerated dose for the dog is 10 mg./Kg./day, while the compound is well tolerated by the monkey at doses of 20 mg./Kg./day. The usual dosage schedule employed in man in clinical studies of Isoniazid as an antituberculous agent is 3–5 mg./Kg./day. The current report is concerned with our experiences with relatively large doses of this compound in the course of a study of the effects of the drug in neoplastic disease.

Five patients received Isoniazid in doses of 20–37.5 mg./Kg./day and were maintained on the drug at these levels for periods of 6 to 70 days without evoking serious adverse reactions. Serial laboratory determinations showed no alteration, and necropsy in 4 patients who died of their neoplastic disease failed to show tissue damage that could be attributed to the drug. Isoniazid plasma concentrations were obtained in 1 case (20.4 γ/ml.), and these concentrations are twice those reported lethal for the dog.

Results suggest that human tolerance for Isoniazid is appreciably greater than that which has been reported for the dog and more closely approximates the degree of tolerance reported for the monkey. A systematic exploration of the therapeutic effects of higher dose levels of Isoniazid is warranted.

The Treatment with Erythromycin of over 100 Patients with Bacterial Pneumonia. *Monroe J. Romansky, J. P. Nasou* and R. E. Ritts.** George Washington University Medical Division, District of Columbia General Hospital, Washington.

Over 100 patients have been studied for evaluation of the effectiveness of erythromycin in bacterial pneumonias. Patients with clinical, radiographic, and laboratory evidence of pneumonia were treated with this agent without selection.

The ratio of lobar to broncho pneumonia was 3:1. The organism was identified by blood culture, sputum culture or smear as pneumococcus in 44% of the cases, and as other organisms in 3% of the cases. Erythromycin was used orally in doses of 100–400 mg. every 3, 4, or 6 hrs. The total dose was 1–5 Gm. for 24%, 6–10 Gm. for 26%, 11–15 Gm. for 28%, and over 15 Gm. for 22% of the patients. Fever subsided in somewhat over 50% of the patients within 48 hrs. of the initiation of treatment. The fever in the majority of the remaining patients had subsided by 72 hrs. Approximately 25% of the patients were treated for 5 days, an additional 25% for 7 days, and the remaining patients required 10 or more days of treatment.

As of the present evaluation (abstract), results were satisfactory in all but 1 case in which the dose was probably insufficient. There were 4 deaths; 3 complicated by delirium tremens, and 1 from pulmonary infarction following successful resolution of the pneumonia. In this group of patients there were no complications such as pleural effusion; empyema did not occur in this series. Toleration of erythromycin was good, and no gross side reactions were noted.

In vitro sensitivity tests done on 64 strains of pneumococci reveal over 70% sensitive to less than 0.1 μg. erythromycin/ml.; 20% sensitive to 0.2 μg./ml.; the remainder sensitive to 0.3 or 0.5 μg./ml.

In this series of more than 100 patients with bacterial pneumonia treated with erythromycin, the results appear to be comparable to those obtained with other antibiotics.

KIDNEY AND URINARY TRACT

Renal Function During Severe Metabolic Acidosis. *Robert L. Jenson,* G. James Tobias,* Joseph F. Greaney,* Arnold S. Relman and William B. Schwartz.* Departments of Medicine, Boston University School of Medicine and Tufts College Medical School; Evans Memorial, Massachusetts Memorial Hospitals and the New England Center Hospital, Boston.

In an attempt to evaluate various aspects of renal function during acute severe acidosis, measurements of inulin clearance (C_{In}), creatinine clearance (C_{Cr}), PAH clearance (C_{PAH}), TmPAH and Tm glucose were made before and several hours after rapid infusion of hydrochloric acid into unanesthetized well-hydrated dogs. Despite an average depression of blood pH to 6.98 and an average reduction of serum carbon dioxide content to 6.2 mEq./L., there were no significant changes in C_{In}, C_{Cr} or C_{PAH}. On the assumption of no change in protein-binding of PAH, TmPAH appeared to be reduced

by 43%, but the maximal tubular transport of glucose was unaffected. It is concluded that acute metabolic acidosis does not impair renal hemodynamics in the dog. The data also suggest that, in the range of pH changes studied, the mechanism for tubular transport of PAH is pH-sensitive, while the mechanism for glucose transport is not. In this respect tubular transport of glucose appears to differ from the process responsible for the over-all removal of injected glucose from the blood.

Potassium Depletion by Prolonged Vivodialysis in the Dog. *Fred Goldner, Jr.,* Gilbert Gordon* and Lawrence G. Raiss** (introduced by *Maurice B. Strauss*). Harvard Medical School, Peter Bent Brigham Hospital, Boston.

Nine dogs were dialyzed with an artificial kidney. In 3 control experiments (14 hrs. of dialysis at 200 cc./min. blood flow) the bath contained normal concentrations of electrolytes. In 6 depletion experiments continued to death (10–21 hrs. at 100–200 cc./min.), potassium was omitted from the bath and bicarbonate concentration was varied. The following findings were common to both control and K-depleted animals: (1) The arterial pH and bicarbonate concentration were usually lower than in the bath. (2) Despite this acidosis, the urine remained alkaline. (3) GFR and ERPF decreased moderately. (4) Progressive hemolysis and periods of hypotension occurred.

In depletion experiments K loss totalled 6–15 mEq./Kg. body weight (average 9.5). Plasma K decreased to about 2 mEq./L. in 2 hours, then declined gradually to 0.5–1.1 mEq./L. terminally. The rate of K loss from cells reached peak values during the first 2 hours and was then sustained. Although renal K excretion decreased markedly, U/P ratios remained greater than 1.0.

Tissue analysis showed a 20% loss of skeletal muscle potassium, but no loss from heart muscle.

K depletion did not lead to alkalosis with acid urine in these experiments. Any such tendency may have been obscured by the experimental procedure itself, since the control animals developed acidosis with alkaline urine.

NEOPLASTIC DISEASE

Clinical Studies with 2, 4-Diamino-5 (3′4′-Dichlorophenyl) 6-Methyl Pyrimidine. *M. Lois Murphy,* Rose Ruth Ellison, David A. Karnofsky,* and J. H. Burchenal.* Chemotherapy Service, Memorial Center for Cancer and Allied Diseases, the Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, and the Sloan-Kettering Division of Cornell University Medical College, New York.

An antagonist of the folic acid-citrovorum factor system, 2, 4-diamino-5(3′4′-dichlorophenyl) 6-methyl pyrimidine (BW-50-197), structurally related to the antimalarial, Daraprim, has been studied in 44 patients with neoplastic disease.

The inhibition of growth of *L. casei* caused by this compound was reversed by folic acid or citrovorum factor, but in animals toxicity was prevented to a limited extent only by citrovorum factor. 50–197 was shown to have inhibitory effects on the growth of Sarcoma 180 and transplanted leukemias in mice. In patients, marrow depression with many cells resembling megaloblasts, severe ulceration of the buccal mucosa, diarrhea, and frequent rashes were noted.

One patient in whom the maximum tolerated dose had been previously determined, tolerated a 6-fold increase in the dose of 50–197 without toxicity while receiving citrovorum factor intramuscularly simultaneously.

Clinical and hematologic remissions occurred in 3 of 14 untreated children with acute leukemia. Eleven acute leukemic children, resistant to amethopterin or cortisone, and 8 acute leukemic adults showed leucopenia without accompanying marrow or clinical improvements.

Although this drug may affect the folic acid citrovorum factor system at slightly different loci than amethopterin, it therapeutically achieved nothing that amethopterin could not, and since its administration was accompanied by marked evidence of toxicity such as rash, marrow depression, and gastrointestinal ulceration, it is not considered to be a practical agent in the treatment of acute leukemia.

PHARMACOLOGY AND THERAPEUTICS

Mercurial Diuretics in the Treatment of Bromide Intoxication. *Allen E. Hussar and Howard L. Holley.* Montrose, New York City and Birmingham, Alabama.

The aim of treatment of chronic bromide intoxication is the quick elimination of the bromide ion from the system. Until the present time, the administration of sodium chloride has been the standard therapeutic regime. This method is based on the fact that chlorides displace bromide ions when

bromides are withheld and chlorides furnished to the body tissues. The liberated bromide is then excreted in the urine. This treatment of bromism, however, has not been very satisfactory, because the bromides are eliminated slowly, making the recovery period from symptoms prolonged.

The object of our investigation was to determine the value of mercurial diuretics in the treatment of bromism. The studies were carried out on 11 patients hospitalized with chronic bromide intoxication. The urinary excretion of bromide was measured during the administration of sodium chloride, ammonium chloride and mercuhydrin, singly, and in various combinations. These well-controlled experiments furnished the following results: (1) Sodium chloride and ammonium chloride were about equally effective in the elimination of bromides. (2) Mercuhydrin, when given alone, increased urinary bromide excretion about 3-fold. (3) Mercuhydrin, when given to patients receiving sodium chloride therapy, further increased bromide excretion by an average of 60%. (4) Mercuhydrin, when given to patients receiving ammonium chloride, further increased bromide excretion by an average of 130%.

The observation that the combination of ammonium chloride and mercuhydrin proved twice as effective as sodium chloride plus mercuhydrin could be anticipated. Besides furnishing the chloride ions necessary to replace bromides, ammonium chloride also potentiates the action of mercuhydrin.

In view of these findings, we consider the combination of ammonium chloride with a mercurial diuretic the presently-known most effective method to eliminate bromides from the system. The recommended treatment schedule is the administration of ammonium chloride, 6 Gm. per day, and the intramuscular injection of 2 cc. of mercuhydrin every 2nd or 3rd day.

RESPIRATORY SYSTEM

The Effects of Nalline in Normals and in Patients with Respiratory Depression. *A. Salomon,* P. S. Marcus,* J. A. Herschfus and M. S. Segal.* Department of Medicine, Tufts College Medical School and the Departments of Inhalational Therapy and Anesthesiology, Boston City Hospital, Boston.

N-allylnormorphine (Nalline) was administered to 24 patients, 15 of whom suffered from respiratory depression induced by various agents, and to 5 additional volunteer normal subjects. Nalline was administered intravenously; the initial dose of 5 to 10 mg. was frequently followed by a slow intravenous infusion of 5% glucose in water containing additional 5 to 10 mg. Nalline. Observations on the circulatory and respiratory system were made.

1. Thirteen patients with severe respiratory depression induced by natural or synthetic opiates were treated. Their respiratory rate was 10 or less per minute, cyanosis was present in all and 2 patients had Cheyne-Stokes respiration. In several patients the blood pressure and pulse rates were markedly lowered or elevated. Intravenous Nalline increased the respiratory rate to 14 or higher, respirations became deeper and regular and cyanosis disappeared. Blood pressure and pulse returned to their previously established levels. The patients became more responsive. Myosis, however, failed to show a prompt response to normal.

2. Two patients who had received intravenous Demerol postoperatively were in a state of unduly prolonged sleep, though without respiratory depression. Nalline was administered and they immediately became alert and responsive.

3. Two patients with chronic pulmonary emphysema and hypoxia were given 3/8 to 1/2 gr. of morphine sulfate experimentally. The respiratory depression which followed responded promptly to intravenous Nalline. Both of these patients exhibited excitement which lasted 15 to 20 minutes following the intravenous Nalline.

4. Three young patients with barbiturate poisoning (suicidal attempts) in coma, demonstrated diminished deep tendon reflexes but did not exhibit depression of respiratory depth or rate. Intravenous Nalline did not appear to exert any beneficial effect.

5. Four patients under the influence of intravenous sodium pentothal were given Nalline postoperatively in an attempt to shorten the awakening period and to counteract the mild respiratory depression observed in 1 of the patients. Intravenous Nalline did not appear to exert any beneficial effect.

6. Five normal volunteers were given 10 mg. of intravenous Nalline. It caused marked sedation, myosis, a slight decrease in the respiratory rate, resting minute ventilation, timed vital capacity and maximal breathing capacity. These changes lasted from 40 to 90 minutes; the sedative effect lasted for 150 to 240 minutes.

The Alveolar-Arterial Oxygen Pressure Gradient in Parenchymatous Disease of the Liver. *Walter H. Abelman, Jean M. Verstraeten,* N. Robert Frank, William F. McNeely* and Henry J. Kowalski,* Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

The occurrence of arterial oxygen unsaturation in patients with advanced cirrhosis was confirmed, and oxygen transport was further analyzed by the determination of alveolar-arterial oxygen pressure

gradients (according to Riley) in 11 patients with evidence of parenchymatous disease of the liver, breathing room air at rest. Five alcohol addicts with advanced Laennec's cirrhosis (Group I) showed a mean A-A gradient of 35 mm., with a standard deviation of 4.3 mm. Six patients with hepatic enlargement and/or laboratory evidence of hepatic dysfunction (Group II), but without the clinical picture of cirrhosis, had a mean A-A gradient of 17 ± 6.9 mm. Comparisons of these two groups with each other and with 10 normal subjects with a mean A-A gradient of 9.7 ± 4.3 mm. reveal that the difference of the means is significant for each pair ($P = <0.01$).

The mean arterial oxygen tension for Group I was 69.6 ± 5.6 mm., being significantly lower than the mean for the normal group ($P = <0.01$). Arterial oxygen tensions in Group II varied considerably; the mean did not differ significantly from the normal.

None of the patients showed clinical or radiologic evidence of heart or lung disease. The ratio of dead space to tidal volume was generally normal, indicating normal distribution of inspired air. Two of the cirrhotics had less than 11.5 Gm. % hemoglobin (9.6 and 8.6 Gm. %).

While these studies do not permit any conclusions as to the cause of the increased alveolar-arterial oxygen pressure gradients observed in patients with hepatic disease, abnormal venous admixture rather than abnormal diffusion is suspected, but remains to be confirmed by studies at 2 levels of inspired oxygen.

The Differentiation of Arterial Oxygen Unsaturation Caused by Disease of the Lung from that Due to Veno-Arterial Shunting by the Responses to Breathing Pure Oxygen. *J. W. Dow, C. S. Burwell,* L. Dexter and J. D. Whittenberger.* Harvard Medical School, Peter Bent Brigham Hospital, Boston.

Arterial oxygen unsaturation may result from: (1) equilibration of blood in the pulmonary capillaries with oxygen at reduced pressure in the alveoli due to imperfect ventilation of the lung, (2) failure to equilibrate blood in the capillaries with a normal alveolar oxygen pressure, and (3) the addition of venous blood directly to the arterial stream.

When pure oxygen is breathed at ordinary barometric pressure, blood reaches the lung at an oxygen tension ranging from 650–670 mm. Hg. This is true in the normal, in the presence of an abnormal barrier to diffusion, and in all except the most severe cases of ventilatory difficulty. At such high tensions, hemoglobin is fully saturated with oxygen, and in addition there is a calculable amount of oxygen in physical solution. The ratio of total oxygen, combined plus dissolved, divided by the oxygen capacity of the hemoglobin is greater than 1, and may be expressed as a % greater than 100. Thus, for each oxygen capacity and in the absence of shunting, the % saturation of arterial blood that should be reached during ventilation with pure oxygen is known.

When a patient with a veno-arterial shunt breathes pure oxygen, blood from aerated parts of the lung is equilibrated at the same high oxygen pressure, and contains a known amount of oxygen. If the lung is normal, the new pulmonary venous oxygen content constitutes a calculable increase over the content during ventilation of the lung with air. It is further demonstrable that, if oxygen consumption and pulmonary flow are the same while breathing the 2 gases, the increase in systemic arterial oxygen content must equal the increase in pulmonary venous oxygen content. Therefore, in the presence of a veno-arterial shunt without complicating pulmonary factors, the rise in arterial oxygen saturation may be predicted for blood of any hemoglobin content.

Curves may be constructed to represent: (1) the % of saturation that should be reached while breathing pure oxygen for blood of any oxygen capacity in the absence of veno-arterial shunt, (2) the % of increase in arterial saturation to be expected when unsaturation is due to shunting without pulmonary disease. If arterial saturation while breathing pure oxygen approximates the first curve, the fault must have been with the lung alone. If the rise approximates the second curve, the observed unsaturation may be regarded as wholly due to shunt. Increases in saturation intermediate between the 2 curves indicate a combination of shunting and pulmonary disease.

Notices of Importance to Investigators

EDITORIAL

Concerning Local Research Groups

ONE WHO IS INTERESTED in the promotion of scientific investigation may occasionally be allowed to reflect upon the conditions which stimulate original thought. We shall use this as license to remark upon the well-known fact that Western Civilization has produced short periods of intense intellectual activity, which have alternated with long periods of inactivity, and that the outbursts of greatest activity have taken place in small areas, and over periods of time that are brief when measured on the scale of history. Greece in the "Golden Age," Italy during the Renaissance, and Western Europe during the past two centuries were places and times of such intellectual vigor. It is very interesting that these were not places and times of political and social stability. They were places and times of great social ferment in societies which were divided into many small competing city states, or somewhat larger but equally competitive national states, constantly striving against each other in commerce, war, sports, science, chicanery, art, and almost every other field of normal human activity.

Your Editor would be read out of the Federation if he leaped to the conclusion that political fragmentation and social turmoil are essential to creative thought, but he stands upon his right to speculate that there may be a correlation between the two. He suggests that the basis for this correlation, if it exists, lies in the fact that in these places, and at these times, men were gathered together in small, independent groups, temporarily free from past cultural restrictions, actively engaged in sharing their ideas with each other, strenuously competing with other similar groups, and quickly rewarding their colleagues for excellence in the competition.

We do not live in an era of city states today, or even in an era of national states, as the eighteenth century knew that term. Ours is a "continental state," in a world increasingly dominated by continental states, each as large as the Roman or Persian empires, and each becoming rapidly much less diverse. Possibly we face the danger of a form of intellectual paralysis which ultimately affected these old societies—a danger that our intellectual activities will become centralized in a few large cities, which will so dominate the climate of our national thinking that originality and creativeness will suffer. There are some who detect a trend toward this in the increasing planning and centralization of research activities which have taken place during the past decade.

It may not be out of place to suggest that the Local Research Group can serve a purpose of high value to us all, and that the greatest service which the Federation can render lies in the stimulation of its members to gather themselves into such groups. The founders of the Federation believed this. They had one major idea in mind: they wanted to give to young and creative men an opportunity to share their ideas with each other. From the very first they were as much interested in stimulating local groups as they were in developing the national group. The principles which they laid down for the formation of such groups still appear to be entirely sound.

They agreed that each group should be the judge of its own membership requirements, and that any man should be admitted who

could satisfy his fellows that he had a sincere interest in research connected with medicine. They agreed that local groups could collect their own dues (if any), elect their own officers, and hold their meetings when and how they saw fit. They agreed that members of local groups need not be members of the National Federation, and that if local group members wished to become National members they should make their individual application to the Council of the National Federation. They hoped that many members of local groups would become National members, and they hoped that each local group would report its activities annually to the National Secretary; but most of all they hoped that men would get together throughout the country, to discuss their problems, to criticize and stimulate each other, and to create that competitive intellectual spirit in their community which seems to bring out the best in those who work with their minds. For, despite popular opinion, scientists do not thrive in lonely barns; they do best in groups, and nourish themselves upon each other's thoughts—sometimes to a disconcerting degree.

These broad and flexible rules for the formation of local groups are still in effect. The National office always stands ready to give assistance to those interested in their formation.

Notices to Members

The National Meeting will be held at the Steel Pier Theatre, Atlantic City, N. J. on Sunday, May 2, 1954. Convention Headquarters will be at the Haddon Hall Hotel, as has been customary in the past.

A meeting of the Council was held on October 29, 1953 in Chicago, following the meeting of the Midwestern Section of the Federation. This meeting was concerned primarily with the problems connected with the unexpectedly rapid growth and development of our journal. The steady increase in the number of members of the Federation, and in the number of abstracts submitted to the various meetings, brought up questions which required decisions by the Council as a whole.

Four issues of CLINICAL RESEARCH PROCEEDINGS will appear in the forthcoming year. Three of these will appear in the spring (March, April, June) and one in the fall (September). This increase in the number of issues will make it possible to take care of the increased number of abstracts, to make certain savings in the cost of publication of individual issues, and to publish our material more rapidly. The present issue contains the abstracts submitted to the meeting of the Midwestern Section in October 1953, and those submitted to the meeting of the Eastern Section in January 1954.

The second issue, containing the abstracts submitted to the National Meeting, will be available for the members at the time of the meeting in May. Copies will also be for sale at the door.

A Note of Appreciation

On behalf of the Council, the Editor wishes to express appreciation to the following concerns for their recent help to certain National activities of the Federation.

Sharp & Dohme, Division of Merck & Co., Inc.

Burroughs and Wellcome & Co. (U.S.A.) Inc.

Ciba Pharmaceutical Products

We also wish to express our gratitude to our publishers, Grune & Stratton, for their foresight in enabling us to establish this publication, and their unselfish spirit in continuing it on an expanded basis.